Title: Improving Adolescent Health Through Immunisation: A Case Study - Invasive Meningococcal Disease

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by

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ABSTRACT

Immunisation is considered as one of the most cost-effective and successful disease prevention strategies. Immunisation during the adolescent period requires additional evaluation because of lower uptake of recommended vaccines compared with childhood immunisation, and the important role of adolescents in indirect protection and transmission of infection to others. This may be particularly pertinent for invasive meningococcal disease (IMD), where adolescents have high rates of IMD, attributed in part due to their higher pharyngeal carriage rates of the bacteria compared to others in the community. The inclusion of a new meningococcal B vaccine on the national immunisation program for direct protection of adolescents has been rejected in Australia due to uncertainty in cost-effectiveness analysis.

By focusing on the above issues, this PhD thesis comprises four peer-reviewed published papers and two manuscripts, that have contributed to a better understanding of adolescent views and preferences for vaccination and the burden of IMD as a case study. This PhD project aims to answer four research questions:

1. What are adolescent views about immunisation and how do they differ from adult views?
2. What are adolescent preferences for vaccination programs and what are the most important factors influencing their decisions?
3. What is known about the disease burden and consequences of IMD, a severe infection with adolescence a peak risk period?
4. What is the mean lifetime cost of IMD per patient taking healthcare system and societal perspectives?

To evaluate adolescent views and perception about vaccines, a national online survey was conducted in adolescents and adults to assess and compare their views on vaccine benefits, community protection, risks, side effects, sources of information, and decision-making preferences. By using the first three survey questions to predict participants' vaccine hesitancy, a higher level of vaccine hesitancy was demonstrated in adolescents in comparison with adults (Odds Ratio=1.44, 95%CI: 1.01, 2.04, p=0.043). Adolescents were more concerned about vaccine side effects than adults for potential side effects including pain (p<0.001), redness or swelling (p<0.001), and fever (p=0.006). To make a vaccine decision, adolescents were more likely to prefer a joint decision with parents (Relative Risk Ratio=1.78, 95%CI: 1.41, 2.25, p<0.001) or make the decision themselves (Relative Risk Ratio=2.24, 95%CI: 1.25, 4.03, p=0.007) than adults.

A discrete choice experiment design was used in a second online survey to evaluate adolescent preferences for vaccination. Stronger preferences were observed for vaccination in the case of a life-threatening illness (p<0.001), lower price vaccinations (p<0.001), mild but common side effects (p=0.004), delivery via a skin patch (p<0.001) and vaccination administered by a family practitioner (p<0.001). Participants indicated that they and their families would be willing to pay AU$394.28 (95%CI: AU$348.40, AU$446.92) more for a vaccine targeting a life-threatening illness than a mild-moderate illness, AU$37.94 (95%CI: AU$19.22, AU$57.39) more for being vaccinated at a family practitioner clinic than a council immunisation clinic, AU$23.01 (95%CI: AU$7.12, AU$39.24) more for common but mild and resolving side effects compared to rare but serious side effects, and AU$51.80 (95%CI: AU $30.42, AU$73.70) more for delivery via a skin patch than injection.

Published literature that reported the clinical and financial burden of IMD was reviewed. Meta-analyses were performed to assess the effect of age and serogroup on case fatality rates (CFRs) of IMD. All costs associated with IMD were converted into international dollars (I$) to compare costing data across studies. The pooled overall CFR was 8.3% with the highest pooled CFR in serogroup W cases. The predicted CFR was higher in adolescents compared with young children. Presence of sequelae (complications) was associated with significantly higher hospitalisation costs. Most commonly reported sequelae were arthritis, neurocognitive sequelae, hearing loss, seizures, speech/communication problems, and amputation. The mean costs of acute admission ranged from I$1,629 to I$50,796.

To estimate the lifetime costs of IMD, a cohort-based state-transition model (Markov) was developed. A comprehensive clinical and health economic literature review and expert panel discussion were used to develop the model structure. Selections of model parameters including age-specific mortality rates, and probabilities of IMD-related sequelae were based on a systematic review or best available evidence. The undiscounted lifetime societal cost per IMD case is US$319,897 including the direct healthcare cost of US$65,035. Given a 5% discount rate, the costs are USD$54,279 and USD$13,968 respectively. Chronic renal failure and limb amputation result in the highest direct healthcare costs per patient. Patients aged <5 years incur the higher healthcare expenditure compared with other age groups. The costing results are extremely sensitive to the discount rate and disease incidence.

In this doctoral study, adolescents demonstrated lower levels of vaccine confidence than adults, but preferred vaccine strategies for a life-threatening disease. The vaccine preventable disease, IMD, although uncommon and occurring primarily in young children

and adolescents, imposes a substantial clinical and financial burden on patients, their families and society. Improving vaccine confidence and providing publicly funded vaccines are important factors that may positively affect vaccine uptake in adolescents.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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PUBLICATIONS CONTRIBUTING TO THIS THESIS

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Wang B, Chen G, Ratcliffe J, Haji Ali Afzali H, Giles L, Marshall H. Adolescent values for immunisation programs in Australia: A discrete choice experiment. *PLOS ONE* 2017; 12(7):e0181073

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Wang B, Giles L, Haji Ali Afzali H, Clarke M, Ratcliffe J, Chen G, Marshall H. Adolescent confidence in immunisation: Assessing and comparing attitudes of adolescents and adults. *Vaccine* 2016; 34(46):5595-603.

Cited 3 times (Scopus 30 October 2018). Journal 5 year Impact Factor 3.309 (ISI web of knowledge InCites Journal Citation Reports Edition 2017)

Marshall H, **Wang B**, Wesselingh S, Snape M, Pollard AJ. Control of invasive meningococcal disease: Is it achievable? *International Journal of Evidence-Based Healthcare* 2016; 14(1): 3-14.

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To be submitted for publication:

Wang B, Afzali H, Giles L, Marshall H. Lifetime costs of Invasive Meningococcal Disease: A Markov model approach

CONFLICT OF INTEREST

The cost of the online survey in Section 2.2 was funded by a general research project grant provided by Novartis Vaccines and Diagnostics Pty Ltd. However, this was an investigator led study, designed and conducted independently of the sponsors with the analyses and writing of the publication completed by the listed authors. The decision to submit the manuscript for publication was made by the authors.

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
CFR	Case fatality rate
DCE	Discrete choice experiment
GP	General practitioner
HPV	Human papillomavirus
IMD	Invasive meningococcal disease
MenACWY	Meningococcal serogroup ACWY
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
NIP	National Immunisation Program
PBAC	Pharmaceutical Benefits Advisory Committee

CHAPTER 1 THESIS OVERVIEW

1.1 BACKGROUND

Suboptimal vaccine uptake in adolescents has been increasingly recognised as an important public health issue [1]. Strategies to achieve optimal uptake in this age group have become a priority in the public health sector [1-3]. Engaging adolescents in decisions affecting their health is vital to build a safe and healthy passage from adolescence into adulthood and parenthood [4]. The prevalence of health risk behaviours rises markedly during adolescence as individuals become gradually responsible for their own health [5]. The views and values of adolescents in immunisation are seldom investigated [3,6-12] and yet their opinions may impact the success of adolescent health programs [13]. The systematic incorporation of adolescent views will improve their health by developing disease prevention programs tailored to their needs [14]. Evaluating vaccine perception and preferences in adolescents, can inform strategies to improve vaccine uptake in this age group. Given the importance of vaccine uptake and research gap identified in the literature, this PhD project aims to investigate adolescent views and preferences towards vaccination.

Prior research has found disease severity was one of the key drivers influencing vaccine decisions in parents and adults [15-17]. In one qualitative study that included a youth jury, adolescents listed life-threatening diseases as a key priority for determining vaccine funding decisions [13]. Since Invasive meningococcal disease (IMD) is a serious infection and meningococcal serogroup B (MenB) vaccines have not been nationally funded yet mainly because of lack of strong economic evidence, the burden of IMD has been further investigated as a case study.

IMD is a life-threatening disease due to its rapid onset and potentially severe outcomes. Although IMD is uncommon, the disease is a significant public health concern. Secondary to infants and young children, adolescents are at increased risk of IMD with a high case fatality rate (CFR) compared to other age groups [18,19]. IMD is caused by a Gram-negative bacterium *Neisseria meningitidis*. The bacteria can cause meningitis, septicaemia or a combination of both. Around 10% of the healthy population carry and spread the bacteria asymptomatically [20]. People who develop IMD often have non-specific symptoms including sudden onset of fever, general malaise, cold hands, thirst, joint pain, aching muscles, headache, neck stiffness, photophobia, nausea, vomiting, drowsiness and coma. The development of the typical rash usually occurs late in the illness. Despite timely antibiotic therapy, the overall CFR in Australia is approximately 5% [21]. IMD can cause sequelae in up to 58% of children who survived the infection [22]. Thirteen serogroups are characterised and serologically defined: A, B, C, D, E, H, I, K, L, W, X, Y, and Z. Five primary serogroups (A, B, C, W and Y) and more recently X cause almost all cases of IMD globally [23,24]. IMD is a vaccine preventable disease. Adolescent immunisation can provide direct protection and generate potential herd immunity. Vaccines are available to protect against five major serogroups: A, B, C, W and Y. Three types of meningococcal vaccines are available in Australia [25]. The meningococcal serogroups ACWY (MenACWY) vaccine is listed on the National Immunisation Program (NIP) for adolescents aged 15-19 years from 01 June 2019 due to a recent rise in serogroup W (MenW) disease.

- recombinant MenB vaccines - for protection against serogroup B disease: Bexsero®, Trumenba®
- quadrivalent (A, C, W, Y) meningococcal conjugate vaccines - for protection against four serogroups of IMD: Menactra®, Menveo®, Nimenrix®

- meningococcal C (MenC) conjugate vaccine vaccines - for protection against serogroup C disease: Menitorix® (combination formulation with the Haemophilus influenzae type b (Hib-MenC) vaccine), NeisVac-C® (monovalent meningococcal C vaccine)

This research has been undertaken in the Australian context, where meningococcal vaccine funding in adolescents as part of the NIP is being considered (MenB vaccine) or has been decided (MenACWY vaccine). Adolescent views and preferences towards vaccination can assist in developing new strategies to improve vaccine uptake after the roll-out of a new vaccine program in adolescents. The results of online surveys in Chapter 2 can also assist in determining vaccine coverage estimates which are important parameters in health economic models. For example, the predicted high coverage rate of vaccination against a life-threatening illness, may positively affect outcomes of health economic evaluation. Assessing the disease burden (both clinical and financial) of IMD, for which a new MenB vaccine program is being considered at a national level, can inform future cost-effectiveness analyses and public funding decisions.

1.2 RESEARCH QUESTIONS AND HYPOTHESES

The overall aim of this PhD thesis is to provide useful information and valuable insights into vaccine attitudes and the burden of a vaccine-preventable disease to improve adolescent health through immunisation. This PhD project aims to address the following research questions:

1. What are adolescent views about immunisation and how do they differ from adult views? (Paper 1 in Section 2.2)

   The World Health Organization (WHO) defines adolescents as those people between 10 and 19 years of age [26]. Adolescents aged between 15 - 17 covering year 10 to year 12 of high school in Australia were enrolled in the online survey. Since vaccine attitudes were compared between adolescents and adults, this online survey did not focus on a specific vaccine for adolescents (e.g. meningococcal or HPV vaccines). General views about immunisation were investigated.

   Three specific hypotheses were investigated in Paper 1, namely:
   H1: Higher concerns about vaccine safety and lack of vaccine confidence in adolescents lead to low vaccine uptake.
   H2: Social media is used as a main source of information in adolescents.
   H3: Parents make vaccine decisions for their children. Adolescent involvement in the decision-making process is minimal.

2. What are adolescent preferences for vaccination programs and what are the most important factors influencing their decisions? (Paper 2 in Section 2.3)

As the research objective was to assess their preferences for vaccination including locations such as schools or universities, 15-19 year olds were enrolled to cover students in years 10 through 12 of high school or in the first year of university.

Two hypotheses were considered as part of this research question:

H4: Adolescents prefer vaccines against serious (life-threatening) infections or sexually transmitted infections with individual and community protection, common but mild side effects, delivery via oral dose/skin patch and being administered at school/university.

H5: Vaccine prices influence their vaccine decisions, although for most adolescents their living and medical expenses would be paid by parents.

3. What is known about the disease burden and consequences of IMD? (Paper 3 in Section 3.1.1, Section 3.1.2, and Paper 4 in Section 3.1.3)

The overarching hypothesis investigated in these sections was:

H6: IMD is associated with high mortality and morbidity rates.

4. What is the mean lifetime cost of IMD per patient taking healthcare system and societal perspectives? (Paper 6 in Section 3.2)

The hypothesis investigated in this paper was:

H7: The societal and healthcare costs associated with long-term sequelae are substantial.

1.3 THESIS OUTLINE

Chapter 2 focuses on research gaps in adolescent immunisation. Results including preferences for vaccines against life-threatening diseases were obtained from two online surveys evaluating adolescent views and preferences towards vaccination in general (Papers 1 and 2). The first online survey assessed and compared vaccine attitudes in adolescents with adults. Adolescents showed a higher level of vaccine hesitancy than adults, as reflected by low vaccine uptake in adolescents. It was also found that adolescents were eager to engage in the vaccine decision-making process. Vaccine preferences were further investigated in the second online survey using a discrete choice experiment (DCE) design. Adolescents expressed strong preferences for vaccination against a life-threatening illness. The vaccine price would affect their decision too. Chapter 2 provides information on how to improve vaccine uptake. The results can be potentially used to determine important parameters (e.g. vaccine coverage) in health economic models and support the results of health economic evaluations. Strategies to improve vaccine uptake are also important for cost effectiveness evidence.

As IMD is a serious infection with high mortality and morbidity rates, it is a perfect example to use for evaluation of the disease severity from clinical and financial perspectives. In Chapter 3, the burden of IMD and development of meningococcal vaccines were investigated and reviewed. A systematic review was conducted to comprehensively estimate the clinical and financial burden of IMD. Meta-analyses were performed to investigate the effects of age and serogroup on CFRs. The results are presented in Paper 3. The sequelae and complications associated with IMD were also included in the systemic review and summarised in Section 3.1.2. The review results in regard to the financial burden of IMD (Paper 4) were published in a highly ranked international health economic journal. The development and current status of vaccines that provide protection

against five major serogroups of IMD (A, B, C, W and Y) were reviewed and published (Paper 5). Paper 6 describes lifetime costs derived from a decision analytic model. Given its severity, IMD has been selected to generate evidence to better inform future cost-effectiveness evaluations. The MenB vaccine programs for infants and adolescents have not been included on the NIP in Australia. Evidence of the considerable burden of IMD can assist in informing government funding decisions. The MenB vaccine programs for adolescents are publicly funded in South Australia. The results regarding outcomes of IMD can be used to reduce vaccine hesitancy in adolescents.

Chapter 4 discusses the possible contribution to the scientific literature, potential implications and translation of study results, and the directions of future work. Chapter 5 summarises the main findings of this PhD project.

CHAPTER 2: ADOLESCENT IMMUNISATION

2.1 LITERATURE REVIEW

It is often stated that immunisation is one of the most cost-effective public health strategies which enormously contribute to global health [27]. A major success story is the eradication of smallpox with massive mortality in the pre-vaccination period. In Australia, the first publicly funded vaccine (diphtheria-tetanus-pertussis) was introduced in 1953. The first national immunisation schedule was implemented in 1975 [28]. Immunisation has become a major public health strategy funded by state and federal governments. Since the introduction of immunisation in Australia, the incidence of vaccine preventable diseases, such as tetanus, diphtheria, haemophilus influenzae type B and measles, has fallen dramatically [29]. After the implementation of the national MenC vaccine program in 2003, the incidence of MenC disease has declined considerably, with the number of cases decreasing from 162 in 2002 [30] to 14 in 2017 [31]. The current NIP (Figure 1) consists of a schedule of recommended vaccines in different age groups, which covers 16 diseases, including hepatitis B, diphtheria, tetanus, pertussis, Haemophilus influenzae type b disease, poliomyelitis, pneumococcal, rotavirus, measles, mumps, rubella, MenC disease, chickenpox, hepatitis A, human papillomavirus (HPV) and influenza. Infants and young children remain the main target population for vaccination programs. However, adolescents have received increasing attention because of 1) new vaccines being available targeting the adolescent age group, 2) low vaccine uptake of vaccines for adolescents compared to children [4]. Improving vaccination uptake in this age group is important to boost immunity, and provide direct protection against diseases in adolescents and the potential for indirect community protection [1].

Figure 1 National Immunisation Program Schedule [32]

(From 1 July 2018)

Age	Disease	Vaccine Brand
Childhood vaccination (also see influenza vaccine)		
Birth	• Hepatitis B (usually offered in hospital)[a]	H-B-Vax® II Paediatric or Engerix B® Paediatric
2 months Can be given from 6 weeks of age	• Diphtheria, tetanus, pertussis (whooping cough), hepatitis B, polio, *Haemophilus influenzae* type b (Hib) • Pneumococcal • Rotavirus[b]	Infanrix® hexa Prevenar 13® Rotarix®
4 months	• Diphtheria, tetanus, pertussis (whooping cough), hepatitis B, polio, *Haemophilus influenzae* type b (Hib) • Pneumococcal • Rotavirus[b]	Infanrix® hexa Prevenar 13® Rotarix®
6 months	• Diphtheria, tetanus, pertussis (whooping cough), hepatitis B, polio, *Haemophilus influenzae* type b (Hib)	Infanrix® hexa
Additional vaccines for Aboriginal and Torres Strait Islander children (QLD, NT, WA and SA) and medically at-risk children[c]	• Pneumococcal	Prevenar 13®
12 months	• Meningococcal ACWY • Measles, mumps, rubella • Pneumococcal	Nimenrix® M-M-R® II or Priorix® Prevenar 13®
Additional vaccines for Aboriginal and Torres Strait Islander children (QLD, NT, WA and SA)	• Hepatitis A	Vaqta® Paediatric
18 months	• *Haemophilus influenzae* type b (Hib) • Measles, mumps, rubella, varicella (chickenpox) • Diphtheria, tetanus, pertussis (whooping cough)	ActHIB® Priorix-Tetra® or ProQuad® Infanrix® or Tripacel®
Additional vaccines for Aboriginal and Torres Strait Islander children (QLD, NT, WA and SA)	• Hepatitis A	Vaqta® Paediatric
4 years	• Diphtheria, tetanus, pertussis (whooping cough), polio	Infanrix® IPV or Quadracel®
Additional vaccines for medically at-risk children[c]	• Pneumococcal	Pneumovax 23®
Adolescent vaccination (also see influenza vaccine)		
• 10-<15 years • (School programs[d])	• Human papillomavirus (HPV)[e] • Diphtheria, tetanus, pertussis (whooping cough)	Gardasil®9 Boostrix®

Age	Disease	Vaccine Brand
Adult vaccination (also see influenza vaccine)		
15 – 49 years Aboriginal and Torres Strait Islander people with medical risk factors[c]	• Pneumococcal	Pneumovax 23®
50 years and over Aboriginal and Torres Strait Islander people	• Pneumococcal	Pneumovax 23®
65 years and over	• Pneumococcal	Pneumovax 23®
70–79 years[f]	• Shingles (herpes zoster)	Zostavax®
Pregnant women	• Pertussis (whooping cough)[g] • Influenza[h]	Boostrix® or Adacel®

Funded annual influenza vaccination[h]
6 months and over with certain medical risk factors[b]
Aboriginal and Torres Strait Islander children 6 months to less than 5 years
Aboriginal and Torres Strait Islander people 15 years and over
65 years and over
Pregnant women

a Hepatitis B vaccine: Should be given to all infants as soon as practicable after birth. The greatest benefit is if given within 24 hours, and must be given within 7 days.
b Rotavirus vaccine: First dose must be given by 14 weeks of age, the second dose by 24 weeks of age.
c Refer to the current edition of The Australian Immunisation Handbook for all medical risk factors.
d Contact your state or territory health service for school grades eligible for vaccination.
e Observe Gardasil®9 dosing schedules by age and at-risk conditions. 2 doses: 9 to <15 years - 6 months mininimum interval. 3 doses: ≥15 years and/or have certain medical conditions - 0, 2 and 6 month schedule. Only 2 doses funded on the NIP unless 12-13 year old has certain medical risk factors.
f All people aged 70 years old, with a five year catch-up program for people aged 71-79 years old until 31 October 2021.
g Single dose recommended each pregnancy, ideally between 28-32 weeks, but may be given up until delivery.
h Refer to annual influenza information for recommended vaccine brand for age.

Infectious diseases contribute to significant burden of disease in relation to epidemiology, morbidity and mortality. Global efforts are focused on improving vaccination programs and developing new vaccines against major and severe infectious diseases such as HIV, malaria, tuberculosis, Respiratory Syncytial Virus, Enterotoxigenic E. Coli, Shigella and Norovirus [33]. In Australia, government funding for vaccine programs has increased from ten million dollars per annum in the mid-1970s to almost half a billion in the early 2010s [29].

All adolescents in Australia aged 15-19 years will receive free MenACWY vaccine in 2019 owing to a continuous increase in incidence of MenW disease [34]. Vaccines against MenB disease, which has been one of predominant serogroups in Australia, have recently been publicly funded by the state government in South Australia partly due to meningococcal epidemiology, serogroup distribution and community concern [35]. However, the publicly funded national MenB vaccine program has been rejected three times based on an assessment of its clinical effectiveness and cost-effectiveness [36]. Two MenB vaccines are currently available on the private market, 4CMenB (Bexsero®) and MenB-FHbp (Trumenba®). The MenB-FHbp vaccine specifically targets adolescents and young adults.

Whilst Australia has one of the highest vaccine coverage rates in the world for its infant and childhood vaccination [37,38], uptake is less impressive for adolescent vaccination (e.g. HPV) [39] and for vaccination against illnesses such as influenza [40], which despite their potential severity, are often perceived as milder illnesses [41]. In Australia, three-dose HPV vaccination coverage rates are steadily increasing, but lower than 80% (72.9% for boys and 78.6% for girls) [39]. The adolescent vaccination coverage rates are suboptimal in other developed countries such as the US and UK. In the US, the National Immunization Survey estimated the national vaccination coverage at 47% for girls and 53% for boys [42]. In the UK, the two-dose HPV vaccination coverage rate is 83.1% for Year 9 girls who completed a course in 2016/17 [43].

It has been found that adolescents prefer to be actively involved in decision making about their health and have an increasing role in the decision-making process, especially as they age and mature [3,44-46]. However, most prior research has concentrated on

parental perception, health workers' preferences, and/or vaccines against specific illnesses such as HPV, influenza, and IMD [7,9,11,12,15,17,41,45-71]. Several qualitative studies have attempted to gain an understanding of adolescent vaccine attitudes, knowledge and decision-making roles [3,10,72,73]. Limited quantitative research has been conducted to investigate general vaccine preferences and identify vaccine hesitancy in adolescents [6,8,44].

In the US, adolescents and parents were asked about general vaccine perceptions including vaccine safety and efficacy and alternative vaccination venues (school, pharmacy, public health department, hospital emergency room, teen clinic, other). The adolescents stated that vaccines were "very effective" (71%) or "very safe" (69%), representing significantly lower figures than the parental respondents (85% and 83%, respectively). Most adolescents preferred to receive vaccines in hospital settings [44]. In five European countries, face to face interviews were performed to assess knowledge and perception of general vaccination in adolescents. A lack of vaccine confidence was identified, as only 40 - 45% of adolescents strongly agreed that vaccination is the best/safest way to prevent diseases. The study found seriousness of diseases (individual protection), physician or parental recommendations and herd immunity were key motivations for vaccination [8], which was consistent with findings in a Belgian study [6]. The aim of the Belgian study was to assess general perception of vaccination and knowledge about vaccines. Although the Belgian study reported that most adolescents understood that vaccination was a good way to protect against diseases, there were considerable misunderstandings about existing vaccines. For example, 20 - 30 % of adolescents believed vaccines protecting against HIV and preventing diabetes were currently available.

The success of immunisation programs relies heavily on high coverage rates to prevent the spread of vaccine preventable diseases. High coverage of a vaccine with potential indirect population protection could impact cost-effectiveness results [74] and is also an important consideration in vaccine funding decision-making. The Joint Committee on Vaccination and Immunisation in the UK have taken account of the potential for indirect population protection in evaluating cost-effectiveness of a MenB vaccine [75]. Furthermore, policy makers are often expected to make decisions about immunisation programs on assumptions about vaccine acceptance with little evidence of societal opinions and concerns regarding such programs. Since adolescents have become a target group for several vaccines in the immunisation program, increasing their awareness and knowledge of immunisation and vaccine preventable diseases has become a priority. Therefore, it is fundamental to conduct research to investigate adolescent views, concerns and preferences towards vaccination and to actively engage them in the immunisation policy.

This chapter aims to answer two research questions: 1) What are adolescent views about immunisation and how do they differ from adult views? 2) What are adolescent preferences for vaccination programs and what are the most important factors influencing their decisions? The next two sections report the results obtained from two national online surveys. The first online survey (Section 2.2) assessed and compared vaccine views and confidence between adolescents and adults and answered the first research question. The second online survey (Section 2.3) quantitatively evaluated vaccine preferences and priorities in adolescents using a DCE design and answered the second research question. A literature review was also conducted specifically for each research question, and these are summarised in the relevant publications.

2.2 VACCINE CONFIDENCE

Adolescent attitudes towards vaccine benefits, risks, sources of information and decision making were assessed and compared with adults in a national cross-sectional online survey. In 2013, 2505 participants completed the online survey including 502 adolescents and 2003 adults. General public perceptions of vaccination were assessed using linear, logistic, ordinal logistic and multinomial logistic regression models. Adolescents showed lower confidence in vaccines and higher concern about potential vaccine reactions than adults. The resulting publication entitled “Adolescent confidence in immunisation: Assessing and comparing attitudes of adolescents and adults”, demonstrated vaccine hesitancy and concerns. Adolescents showed eagerness to be part of the vaccine decision making process with parents or to make vaccine decisions on their own.

Our results show adolescents are less likely to consult a health professional compared with adults for vaccine advice and rather consult their social network. This likely suggests that most adolescents do not have their own health professional they can engage independently for health advice such as a general practitioner (GP). In line with previous research [2,76,77], this finding may reflect a considerable downward trend in health care utilisation from childhood to early adulthood.

2.2.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

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Contribution to the Paper	BW conceived and designed the study, performed data analysis under instruction of LG and prepared the first draft of the manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

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Adolescent confidence in immunisation: Assessing and comparing attitudes of adolescents and adults

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ABSTRACT

Introduction: There is limited knowledge of adolescent views and attitudes towards immunisation. Our study investigated adolescent attitudes to immunisation and compared differences in vaccination attitudes between adolescents and adults.

Methods: This study was a cross-sectional, national online survey. Recruitment was stratified by state and gender to ensure findings were nationally representative. Regression analyses were performed to assess and compare adolescent and adult views on vaccine benefits, community protection, risks, side effects, sources of information, and decision-making preference.

Results: In 2013, 502 adolescents and 2003 adults completed the online survey. Lower levels of vaccine confidence were observed in adolescents with adolescents less likely to believe vaccines are beneficial and/or safe compared to adults ($p = 0.043$). Compared to females, males were less confident of vaccine benefits ($p < 0.05$) but less concern about vaccine side effects ($p < 0.05$). Adolescents were more concerned about vaccine side effects than adults for pain ($p < 0.001$), redness or swelling ($p < 0.001$), and fever ($p = 0.006$). Adolescents were less likely than adults to consider health professionals ($p < 0.001$) and the media (e.g. internet) ($p = 0.010$) as important sources of information, and were more likely to seek information from social networks ($p < 0.001$) including families and schools. Although 62.0% of adolescents agreed that parents should make the decision about vaccination for them, adolescents were more likely to prefer a joint decision with parents ($p < 0.001$) or by themselves ($p = 0.007$) compared with adults.

Conclusion: Adolescents have a lesser understanding of vaccine safety and benefits than adults and have higher concerns about potential vaccine reactions. Improving adolescent awareness and knowledge of the benefits and risks of vaccination through school-based educational programs may improve confidence in and uptake of vaccines for adolescents and increase vaccine confidence in the next generation of parents.

1. Introduction

Adolescent immunisation programs have expanded substantially in developed countries over the last decade with inclusion of publicly funded vaccines such as human papillomavirus (HPV), varicella, hepatitis B, pertussis, and meningococcal vaccines. The success of immunisation programs relies on high coverage rates to protect vaccinated individuals and the community [1]. In countries such as the United States of America (USA) and Australia, although 'fully immunised' coverage rates are high, these figures

Abbreviations: ANOVA, Analysis of Variance; CI, Confidence Interval; EU, European Union; GP, General Practitioner; HPV, Human Papillomavirus; OR, Odds Ratio; RRR, Relative Risk Ratio; SEIFA, Socio Economic Index for Areas; USA, United States America.

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obscure the lower vaccination rates in population sub-groups including adolescents with adolescent immunisation uptake considerably lower for publicly funded vaccines (40–80%) than childhood immunisations (90–95%) [2,3]. This may be because immunisation coverage for young children (e.g. children aged under 10 years) is strongly correlated to parental decisions, while evidence shows that adolescents are more likely to establish their vaccine-related attitudes independently of their parents and hence differ from their parent's attitudes [4–6]. As adolescents are a target group for current and future immunisation programs, evaluating their awareness and knowledge of vaccination is an important priority. Identifying perceived barriers can lead to the development of more effective adolescent immunisation policies aiming to improve uptake.

Previous research has focused on individual vaccines or parental views, showing that parental perception of disease susceptibility and severity, vaccine safety, side effects, lack of vaccine and disease knowledge, multiple injections at a single visit or being confused about the immunisation schedule, could influence parental decisions to accept, refuse or delay vaccination for their children [4,7–12]. Reasons for low uptake of adolescent routine immunisations are poorly described in the literature apart from HPV and influenza vaccines [4,5,8,13–21]. The aim of our study was to identify adolescent views about immunisation and how they differed from adults' views. We also aimed to identify the barriers and facilitators which may influence receipt of recommended vaccines in adolescents now and in the future as potential parents.

2. Methods

2.1. Study design and population

We undertook a national online survey which comprised a series of attitudinal statements relating to views about vaccination.

We aimed to enrol 500 adolescents and 2000 adults (50% with children aged <18 years) in Australia with state and gender stratification to ensure findings were nationally representative. Details of sample size determination and stratification were reported in a previous publication [22]. All participants were recruited through an online panel company, Pureprofile. Parents who registered on the Pureprofile database were contacted and study information was provided if their child was willing to complete the survey and parental consent and adolescent assent was obtained for them to participate in the study. Following parental consent, the parents were asked to turn the computer over to their adolescent child and the adolescent was then guided through the online survey. Independent Pureprofile account holders were approached to recruit potential adult participants and adolescent participants separately. Prior to survey commencement, a pilot study was completed in March 2013 and results were reviewed to assess questionnaire completion. Since no revisions to the questionnaire were required, the pilot data were included in the final analysis.

2.2. Survey tool

A series of survey questions relevant to vaccination (Fig. 1): (1) vaccine benefits, (2) herd immunity/community protection, (3) vaccine risks, (4) side effects, (5) sources of vaccination information, and (6) vaccination decision-making preferences were presented on-line and distributed to participants. For questions on vaccine benefits participants could nominate highly, moderately, slightly, none at all or uncertain. Concerns about vaccine side effects were measured on an eleven point scale, where 0 was no concern and 10 was extremely concerned. For the survey question regarding main sources of information, although participants were asked to rank sources in order, the top ranked source was considered as the primary source and therefore each source was re-coded into two categories: "Yes, the most important source" or "No, not the most important source". The frequency of the primary source was counted for the analysis.

2.3. Predictor variables

The variables were selected on the basis of prior research findings and a literature review of vaccination coverage and attitudinal studies [23–26]. Socio-demographic variables including age, gender, household size, socio-economic status and area of residence (rural or metropolitan) were obtained from participants. For the purpose of comparison, participant age was coded into two categories: 15–17 years (adolescents) and $\geqslant$18 years (adults). The levels of socio-economic status were measured by the Socio Economic Index for Areas (SEIFA) Index of Relative Socio-economic Disadvantage and categorised into tertiles: low (1st–33rd percentile), medium (34th–66th percentile) and high (67th–100th percentile) [27].

2.4. Data analysis

Descriptive results were reported according to socio-demographic characteristics with mean values and standard deviations for continuous variables and percentages for categorical variables. Student's *t*-tests, analysis of variance (ANOVA), and χ^2 tests were performed to assess differences in group means and proportions, as appropriate.

Ordinal logistic regression was used in analyses of vaccine benefits, community protection and vaccine risks, as these outcome measures were assessed on an ordinal scale (e.g. from "not at all/uncertain" to "high"). Since lower levels of vaccine confidence have been observed to be associated with higher levels of hesitancy [24,28–30], the first three survey questions were used to predict participants' vaccine hesitancy. If participants showed lack of vaccine confidence in at least two of three statements, for example, describing vaccines were slightly beneficial, denying vaccine benefits, believing vaccines were not important in protecting the community, reporting vaccines were moderately to highly risky or being uncertain, those participants were considered to be vaccine hesitant. Multivariable logistic regression was performed to assess overall vaccine hesitancy.

The responses to concerns about potential reactions to vaccination (on a 0–10 scale) were treated as continuous outcome variables. Relationships between predictor variables and the vaccine concern variables were investigated using multivariable linear regression. Adjusted regression coefficients (β) were reported from these linear regression analyses. β, the estimator of the slope coefficient, represents the average change in an outcome variable for every unit change in a predictor variable, holding all other variables constant. Each main source of information about vaccines was coded as a binary outcome variable and analysed in a separate multivariable logistic regression model. Predictor variables of vaccine decision-making preference were assessed using multinomial logistic regression. Predictor variables with a p-value < 0.2 in the univariate analysis were selected for multivariable models along with other variables of known research importance [31].

All statistical analyses were performed using Stata version 12 (Stata Corp, College Station, TX) [32]. Predictor variables with a p-value < 0.05 were considered statistically significant in final regression models.

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee in Adelaide, South Australia, Australia.

1. To what degree do you believe that vaccines are beneficial?

☐ Highly ☐ Moderately ☐ Slightly ☐ Not at all ☐ Uncertain

2. How important do you think vaccinations are in protecting the whole community against diseases?

☐ Very important ☐ Important ☐ Not sure ☐ Not important

3. To what degree do you believe that vaccines are risky?

☐ Highly ☐ Moderately ☐ Slightly ☐ Not at all ☐ Uncertain

4. On a scale of 0-10, where 0 means you are not concerned at all and 10 means you are extremely concerned, how concerned are you about the following potential reactions to vaccines:

i. Pain at the site where the injection was given: Enter number 0-10 ☐☐

ii. Redness or swelling at site where the injection was given: Enter number 0-10 ☐☐

iii. Fever (temperature >38 degrees) following vaccination: Enter number 0-10 ☐☐

5. What are your main sources of information about vaccination (if relevant, you may choose more than one option). Where more than one source is identified, please rank in order of usefulness to you (1= most important)?

☐ Health professionals ☐ Family ☐ Friends/Colleagues

☐ School ☐ Internet ☐ TV

☐ Newspaper/Magazine ☐ Others, please indicate: _____

6. For vaccines that are recommended as part of the standard vaccination schedule for children and adolescents, who should make the decision about vaccination?

☐ Parents ☐ Adolescents (aged 12-18)

☐ Joint decision of parents and adolescents ☐ Someone else (e.g. GP)

Fig. 1. Survey questions on perception of vaccination.

3. Results

In total, 2505 participants completed the online survey between March and May 2013 including 502 adolescents, 2003 adults without (N = 1003) or with (N = 1000) at least one child aged <18 years (Table 1). Adult age ranged from 18 to 81 years and adolescents were aged between 15 and 17 years. Participants were primarily from metropolitan (64.9%) and high socio-economic status (41.0%) areas with a slight female predominance (51.4%). Adolescents and adults had a similar gender and socio-economic profile, however more adults were from metropolitan regions (N = 1330, 66.4%) than adolescents (N = 295, 58.8%, p = 0.001). Almost half the adult sample (48.5%) had at least one child aged under 18 years of age.

Table 1
Socio-demographic Characteristics.

	All[a] (N = 2505)	Adolescents (N = 502)	Adults (N = 2003)	*p*-Value
	N (%)	N (%)	N (%)	
Age (Mean (SD))	37.6 (16.9)	16.0 (0.8)	43.0 (14.5)	<0.001
Gender				
Female	1288 (51.4)	256 (51.0)	1032 (51.5)	0.833
Male	1217 (48.6)	246 (49.0)	971 (48.5)	
Household size (Mean (SD))	3.3 (1.4)	4.1 (1.3)	3.1 (1.4)	<0.001
1	233 (9.3)	1 (0.2)	232 (11.6)	<0.001
2	589 (23.5)	35 (7.0)	554 (27.7)	
3	553 (22.1)	133 (26.5)	420 (21.0)	
4	687 (27.4)	185 (36.9)	502 (25.1)	
5+	443 (17.7)	148 (29.5)	295 (14.7)	
Area of residence				
Metropolitan	1625 (64.9)	295 (58.8)	1330 (66.4)	0.001
Rural	879 (35.1)	207 (41.2)	672 (33.6)	
Socio-economic status				
Low (1st–33rd percentile)	619 (24.9)	119 (23.9)	500 (25.1)	0.842
Medium (34th–66th percentile)	851 (34.2)	172 (34.5)	679 (34.1)	
High (67th–100th percentile)	1021 (41.0)	208 (41.7)	813 (40.8)	
State				
New South Wales	831 (33.2)	162 (32.3)	669 (33.4)	0.970
Victoria	639 (25.5)	131 (26.1)	508 (25.4)	
Queensland	483 (19.3)	102 (20.3)	381 (19.0)	
Western Australia	248 (9.9)	49 (9.8)	199 (9.9)	
South Australia	190 (7.6)	37 (7.4)	153 (7.6)	
Tasmania	62 (2.5)	13 (2.6)	49 (2.6)	
Australian Capital Territory	39 (1.6)	7 (1.4)	32 (1.6)	
Northern Territory	12 (0.5)	1 (0.2)	11 (0.6)	

[a] Area of residence and socio-economic status data were missing for one and 14 participants, respectively.

3.1. Perception of vaccine being beneficial

Amongst adults, 68.0% (N = 1362) strongly believed that vaccines were beneficial with 22.2% (N = 445) believing they were moderately beneficial, 6.8% (N = 136) believing they were slightly beneficial and 3.0% (N = 60) disagreeing or uncertain. Compared with adults, a smaller proportion of adolescents (N = 322, 64.1%) strongly believed that vaccines were beneficial with 24.7% of adolescents (N = 124) responding "moderately" beneficial, 6.4% (N = 32) responding "slightly" beneficial, and 4.8% (N = 24) disagreeing or uncertain. The majority of females strongly (69.8%, N = 899) or moderately (21.4%, N = 275) believed in vaccine benefits compared to 64.5% (N = 785) of males believing strongly and 24.2% (N = 294) believing moderately, that vaccines are beneficial.

After adjusting for age category and socio-economic status in the ordinal logistic analysis, the only factor that was significantly associated with perception of vaccine being beneficial was gender (OR = 0.77, 95%CI: 0.66, 0.91, p = 0.002) with males showing less confidence in vaccine benefits. Adolescents showed a trend towards reduced odds of strongly believing that vaccines were beneficial compared to adults (OR = 0.85, 95%CI: 0.69, 1.04, p = 0.105).

3.2. Perception of public health benefit

In total, 1762 participants (70.3%) agreed vaccines were very important in protecting the whole community against infectious diseases. Compared to adolescents, a slightly higher percentage of adults (70.9% (N = 1421) vs 67.9% (N = 341)) strongly supported the importance of the public benefit from vaccination with a further 22.6% (N = 452) (vs 24.1% (N = 121)) indicating "important", 6.5% (N = 130) (vs 8.0% (N = 40)) indicating "not sure"/"not important". Females were more confident of the public health benefit (73.2%, N = 943) than males (67.3%, N = 819) with 21.0% (N = 271) vs 24.8% (N = 302) reporting "important", and 5.8% (N = 74) vs 7.9% (N = 96) reporting "not sure"/"not important".

After adjusting for age category, household size, socio-economic status, and area of residence in the ordinal logistic analysis, the only predictor variable negatively associated with perception of community protection was gender with males having less belief in the public benefits of vaccines (OR = 0.74, 95%CI: 0.63, 0.88, p = 0.001). There was a trend towards adolescents having reduced confidence in the public health benefit of vaccines compared to adults (OR = 0.83, 95%CI: 0.67, 1.03, p = 0.089).

3.3. Perception of vaccines being risky

Only 16.0% (N = 400) of participants completely disagreed that vaccines were risky. Over half (N = 1467, 58.6%) believed that vaccines were slightly risky with one quarter indicating "moderately risky" (N = 418, 16.7%), "highly risky" (N = 111, 4.4%) and "uncertain" (N = 109, 4.4%). A higher proportion of adolescents (N = 36, 7.2%) were uncertain about vaccine risks versus adults (N = 73, 3.6%). There was no significant difference in risk perception for any of the predictor variables in the adjusted analysis.

3.4. Predicted vaccine hesitancy

A total of 216 participants (8.62%) demonstrated vaccine hesitancy, as they were not confident of vaccine benefits and/or safety. After adjusting for age category and other sociodemographic characteristics in a logistic model, adolescents revealed higher odds of being vaccine hesitant than adults (OR = 1.44, 95%CI: 1.01, 2.04, p = 0.043). An increased household size was associated with lower odds of participants being vaccine hesitant (OR = 0.85, 95%CI: 0.76, 0.95, p = 0.003).

3.5. Concerns about potential vaccine side effects

Participants had more concern about systemic adverse effects such as fever (mean score: 4.4) following injection, than local

reactions such as redness or swelling at the injection site (mean score: 3.3) and injection pain (mean score: 3.2) (ANOVA, p < 0.001).

Results of the multivariable linear regression analyses showed adolescents had higher concern about pain (β = 1.29, 95%CI: 1.00, 1.58, p < 0.001), redness or swelling (β = 1.05, 95%CI: 0.77, 1.33, p < 0.001) and fever (β = 0.41, 95%CI: 0.12, 0.71, p = 0.006) following vaccination than adults (Table 2). On average, males had less concern about vaccine reactions including pain (β = −0.28, 95%CI: −0.51, −0.06, p = 0.012), redness or swelling (β = −0.29, 95%CI: −0.50, −0.08, p = 0.008) and fever (β = −0.38, 95%CI: −0.60, −0.15, p = 0.001) than females. Participants with high socio-economic status expressed less concern about fever (β = −0.32, 95%CI: −0.60, −0.03, p = 0.033) and redness or swelling (β = −0.28, 95%CI: −0.55, −0.00, p = 0.047) than those of low socio-economic status. Participants with a larger household size tended to have more concern about fever (β = 0.10, 95%CI: 0.01, 0.18, p = 0.021).

3.6. Main source of information about vaccination

For adults, health professionals (78.4%), family members (7.6%) and the internet (6.2%) were the top three sources of information about vaccination (Table 3). Adolescents reported health professionals (53.6%), family members (30.5%) and schools (10.2%) as the three most important sources.

Compared to adults, adolescents were less likely to consider health professionals (OR = 0.32, 95%CI: 0.26, 0.40, p < 0.001) and the media (OR = 0.57, 95%CI: 0.37, 0.87, p = 0.010) as the most important sources, and were more likely to seek information from social networks including family, friends and school (OR = 5.02, 95%CI: 3.97, 6.35, p < 0.001) (Table 4). Unlike females, males tended to obtain information from social networks (OR = 1.28, 95%CI: 1.03, 1.59, p = 0.028) and were less likely to consider health professionals as a main source of information (OR = 0.76, 95%CI: 0.63, 0.91, p = 0.003). The media, including internet, newspaper, magazine or TV, was less likely to be a main source of information for participants living in rural areas (OR = 0.72, 95%CI: 0.53, 1.00, p = 0.048) compared to those in metropolitan areas.

3.7. Who should make a decision about vaccination?

The majority of participants agreed that parents should make vaccination decisions for adolescents (N = 1685, 67.3%), with 22.5% (N = 563) indicating a joint decision between parent and adolescent was preferable, 2.5% (N = 63) indicating adolescents should make the decision and 7.7% (N = 194) indicating someone

Table 2
Results of multivariable linear regression describing the factors associated with concerns about potential reactions to vaccines.

	Score	Multivariable linear regression		
	Mean (SD)	Coefficient (β)	95% Confidence interval	*p*-Value
Pain at injection site				
Total (N = 2505)	3.23 (2.90)	–	–	–
Age				
Adolescents (N = 502)	4.32 (3.02)	1.29	1.00, 1.58	<0.001
Adults (N = 2003)	2.96 (2.81)	Ref	–	–
Gender				
Male (N = 1217)	3.09 (2.82)	−0.28	−0.51, −0.06	0.012
Female (N = 1288)	3.37 (2.97)	Ref	–	–
Household size				
	–	0.07	−0.01, 0.15	0.081
Redness or swelling at injection site				
Total (N = 2505)	3.27 (2.77)	–	–	–
Age				
Adolescents (N = 502)	4.14 (2.88)	1.05	0.77, 1.33	<0.001
Adults (N = 2003)	3.05 (2.70)	Ref	–	–
Gender				
Male (N = 1217)	3.12 (2.69)	−0.29	−0.50, −0.08	0.008
Female (N = 1288)	3.41 (2.84)	Ref	–	–
Household size				
	–	0.05	−0.03, 0.13	0.186
Socio-economic status				
Low (N = 619)	3.41 (2.86)	Ref	–	–
Medium (N = 851)	3.29 (2.78)	−0.13	−0.41, 0.15	0.366
High (N = 1021)	3.15 (2.71)	−0.28	−0.55, −0.00	0.047
Fever				
Total (N = 2505)	4.41 (2.90)	–	–	–
Age				
Adolescents (N = 502)	4.80 (2.83)	0.41	0.12, 0.71	0.006
Adults (N = 2003)	4.31 (2.91)	Ref	–	–
Gender				
Male (N = 1217)	4.22 (2.88)	−0.38	−0.60, −0.15	0.001
Female (N = 1288)	4.59 (2.91)	Ref	–	–
Household size				
	–	0.10	0.01, 0.18	0.021
Socio-economic status				
Low (N = 619)	4.54 (2.93)	Ref	–	–
Medium (N = 851)	4.51 (2.95)	−0.03	−0.33, 0.27	0.842
High (N = 1021)	4.23 (2.86)	−0.32	−0.60, −0.03	0.033

Table 3
Main sources of information about vaccination.

	Health professionals	Social networks			Media and others			
		Family	Friends/Colleagues	School	Internet	TV	Newspaper/Magazine	Others
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total (N = 2505)	1839 (73.4)	305 (12.2)	43 (1.7)	91 (3.6)	145 (5.8)	41 (1.6)	13 (0.5)	28 (1.1)
Age								
Adolescents (N = 502)	269 (53.6)	153 (30.5)	2 (0.4)	51 (10.2)	20 (4.0)	1 (0.2)	3 (0.6)	3 (0.6)
Adults (N = 2003)	1570 (78.4)	152 (7.6)	41 (2.1)	40 (2.0)	125 (6.2)	40 (2.0)	10 (0.5)	25 (1.3)
Gender								
Male (N = 1217)	861 (70.8)	158 (13.0)	26 (2.1)	50 (4.1)	75 (6.2)	24 (2.0)	9 (0.7)	14 (1.2)
Female (N = 1288)	978 (75.9)	147 (11.4)	17 (1.3)	41 (3.2)	70 (5.4)	17 (1.3)	4 (0.3)	14 (1.1)
Socio-economic status								
Low (N = 619)	456 (73.7)	76 (12.3)	11 (1.8)	21 (3.4)	34 (5.5)	11 (1.8)	3 (0.5)	7 (1.1)
Medium (N = 851)	620 (72.9)	105 (12.3)	10 (1.2)	27 (3.2)	52 (6.1)	17 (2.0)	9 (1.1)	11 (1.3)
High (N = 1021)	754 (73.9)	122 (12.0)	21 (2.1)	42 (4.1)	59 (5.8)	12 (1.2)	1 (0.1)	10 (1.0)
Area of residence								
Rural (N = 879)	658 (74.9)	107 (12.2)	12 (1.4)	33 (3.8)	39 (4.4)	18 (2.1)	3 (0.3)	9 (1.0)
Metropolitan (N = 1625)	1180 (72.6)	198 (12.2)	31 (1.9)	58 (3.6)	106 (6.5)	23 (1.4)	10 (0.6)	19 (1.2)

Note: For each source presented, the number of respondents ranked as the most important (i.e. ranked as the top one) was counted.

Table 4
Results of multivariable logistic regression describing the factors associated with main sources of information about vaccination.

	Health professional			Social networks			Media and others		
	Odds Ratio	95% Confidence interval	P-Value	Odds Ratio	95% Confidence interval	P-Value	Odds Ratio	95% Confidence interval	*p*-Value
Age									
Adolescents (N = 502)	0.32	0.26, 0.40	<0.001	5.02	3.97, 6.35	<0.001	0.57	0.37, 0.87	0.010
Adults (N = 2003)	Ref	–	–	Ref	–	–	Ref	–	–
Gender									
Male (N = 1217)	0.76	0.63, 0.91	0.003	1.28	1.03, 1.59	0.028	1.24	0.95, 1.64	0.119
Female (N = 1288)	Ref	–	–	Ref	–	–	Ref	–	–
Household size	0.99	0.93, 1.06	0.866	1.06	0.98, 1.15	0.133	0.92	0.83, 1.02	0.106
Socio-economic status[a]									
Low (N = 619)							Ref	–	–
Medium (N = 851)							1.17	0.82, 1.67	0.394
High (N = 1021)							0.79	0.54, 1.16	0.231
Area of residence									
Rural (N = 879)							0.72	0.53, 1.00	0.048
Metropolitan (N = 1625)							Ref	–	–

[a] The predictor variables, socio-economic status and area of residence with a p-value > 0.2 in the univariate analysis, were excluded from multivariable logistic regression models of health professional and social networks.

else (e.g. General Practitioner (GP)) should make the decision. For adolescents, more than half reported that parents should make the decision for them (N = 311, 62.0%), with one third preferring a joint decision with parents (N = 160, 31.9%), 3.8% (N = 19) believing adolescents should make the decision themselves and 2.4% (N = 12) reporting someone else. Compared to children, a slightly higher proportion of adults (N = 1374, 68.6%) believed parents should make the decision for their children with 20.1% (N = 403) supporting a joint decision.

In the multinomial logistic model using 'parents should make the decision' as the reference category and adjusting for gender, household size and socio-economic status, adolescents were more likely to report that adolescents should make the decision instead of parents exclusively (RRR = 2.24, 95%CI: 1.25, 4.03, p = 0.007), and to support a joint decision with parents (RRR = 1.78, 95%CI: 1.41, 2.25, p < 0.001) than adults. Males were more likely to report that adolescents should make the decision (RRR = 1.73, 95%CI: 1.03, 2.92, p = 0.039), and they had less interest in making a joint decision between adolescents and parents (RRR = 0.73, 95%CI: 0.60, 0.89, p = 0.002) than females (Table 5).

4. Discussion

Immunisation is one of the most successful public interventions to protect individuals and the community against vaccine-preventable diseases. As adolescents are an important target group for immunisation, our study focused on adolescent confidence, concerns and preference for decision making about vaccination compared with adults.

The majority of both adolescents and adults were strongly supportive of vaccination and reported that vaccines were highly beneficial. Consistent with our findings, studies conducted in the USA [5] and European Union (EU) [15] reported the majority of parents and adolescents were confident of vaccine effectiveness in preventing disease. However, reduced public confidence in vaccination was observed in more than 10% of participants who doubted or denied vaccine benefits and their safety. Similar to our findings, 17% of adolescents and 30% of parents in the USA study did not perceive vaccines to be "very safe" [5]. Even a moderately high percentage of parents who strongly supported immunisation also expressed their concerns over vaccine safety in a large survey in

Table 5
Results of multinomial logistic regression on making a decision about vaccination with 'parents should make the decision' as the reference category.

	Adolescents should make the decision			Joint decision of parents & adolescents			Someone else should make the decision (e.g. GP)		
	RRR	95% Confidence interval	P-Value	RRR	95% Confidence interval	P-Value	RRR	95% Confidence interval	*p*-Value
Age									
Adolescents (N = 502)	2.24	1.25, 4.03	0.007	1.78	1.41, 2.25	<0.001	0.37	0.20, 0.67	0.001
Adults (N = 2003)	Ref	–	–	Ref	–	–	Ref	–	–
Gender									
Male (N = 1217)	1.73	1.03, 2.92	0.039	0.73	0.60, 0.89	0.002	0.87	0.65, 1.18	0.376
Female (N = 1288)	Ref	–	–	Ref	–	–	Ref	–	–
Household size									
	0.84	0.69, 1.03	0.092	1.00	0.93, 1.07	0.965	0.79	0.71, 0.89	<0.001
Socio-economic status									
Low (N = 619)	Ref	–	–	Ref	–	–	Ref	–	–
Medium (N = 851)	1.13	0.55, 2.33	0.730	1.38	1.07, 1.79	0.014	1.06	0.72, 1.56	0.770
High (N = 1021)	1.51	0.78, 2.92	0.224	1.14	0.88, 1.47	0.312	0.90	0.62, 1.32	0.597

the USA [10]. Lower levels of vaccine confidence could lead to vaccine hesitancy [28]. Vaccine hesitant parents might not completely refuse recommended vaccines, but delay vaccination or reject one or more specific vaccines for their children [24]. Lack of confidence may follow adolescents into adulthood, and so could have consequences for parental confidence in vaccine programs in the future.

Adolescents demonstrated lower confidence in vaccine benefits and/or safety than adults. In the EU study, 41% of adolescents selected "not all vaccinations are necessary" as one of the top three reasons for not being vaccinated [15]. In a study from Belgium, 13% of adolescents did not consider vaccination as a safe way to prevent disease [16]. Since there is minimal opportunity for adolescents to experience vaccine-preventable diseases due to the success of vaccination programs, doubts about vaccine necessity are likely to be relevant to non-compliance with vaccination schedules.

Our study results also showed gender and household size were significant factors affecting vaccine confidence. In line with previous research [21], males demonstrated less confidence in vaccine benefits but less concern about vaccine side effects. A number of studies found females were more likely to oppose a specific vaccine, for example, influenza vaccines [33–35]. In those studies, women were expected to have a lower level of influenza vaccine acceptance due to "societal inequality effect" [36]. However, gender differences were not observed or not significant in multivariable regression analyses in other influenza studies [37]. People from big families showed more willingness to support vaccination than those with a small household size. This may be reflection of higher perceived risks of infections in larger households with more children. Adolescents from larger families may have more support in making decisions about vaccination. In contrast, vaccination coverage studies found the large family size was associated with reduced vaccination uptake in Kenya, Belgium and Greece [26,38,39]. However, this is a measure of uptake rather than intended willingness. The different research questions and study population may be the reason for disparity in study results.

Adolescents reported a higher concern about local and systemic vaccine side effects than adults with fever raising the highest concern in our study. The side effects of the vaccine and fear of the needle were the most frequently reported reasons for not getting vaccinated in the EU adolescent study [15]. Moreover, other study results revealed that younger age and female gender were associated with concerns about needle pain [40,41], which is consistent with our findings.

Although the majority of adolescents and adults indicated health professionals and their family were the most important source of information about new vaccines, not surprisingly adolescents sought vaccine information from schools and social networks more frequently than adults. Similar results were reported in the EU and Belgium studies [15,16]. Those findings emphasise that school-based educational programs are imperative and should be strengthened to provide detailed information of vaccine benefits and potential risks of contracting and transmitting vaccine preventable infectious diseases. Previous research also provides evidence that educating students is one of the best practices to improve coverage rates of school-located influenza vaccination [42]. Adolescents are frequent users of the internet and therefore might be expected to seek information from the internet more often than adults. However, our study showed that adolescents were less likely than adults to seek information about vaccination from media sources. A number of qualitative studies have found that adolescents regard themselves as passive participants in the vaccine decision making process [43,44]. This finding may indicate why they might not actively search for information about vaccination on the internet.

Compared with adults, adolescents were more likely to prefer a joint decision with parents about vaccinations or to make a decision on their own. Adolescent's willingness to be involved in the decision-making process has been reported in previous studies. These studies showed more than half of adolescent participants felt "somewhat comfortable" or "comfortable" to make vaccine decisions for themselves [5], parents stated that adolescents influenced their decisions regarding HPV vaccination [4] and the majority of adolescent participants wanted to be part of a discussion with parents and health care providers in regards to HPV vaccination [6]. The active role that adolescents play in decision making is important and should not be underestimated, as literature shows that greater adolescent involvement in decision making is likely to lead to higher treatment adherence and compliance [45–47].

Our study results are subject to some limitations associated with study design and methodology. Although this is a large national survey with gender and state stratification, the online survey necessitated internet access which may imply a higher participant socio-economic and educational level, thereby impacting upon the generalisability of the study results. This is a web-based survey that ensures anonymity. As such, we could not link survey data with vaccination records to further investigate the relationship between attitudes and vaccine acceptance. Although we aimed to enrol participants independently, we could not verify their relationship between each participant. Social desirability bias may also affect our results. However, participants were informed that data were collected anonymously to minimise socially desirable responses.

Our results showed a lack of confidence in vaccine safety and benefits in a reasonably large proportion of adolescents and adults. Adolescents did not demonstrate better understanding of vaccine benefits or safety, showed higher concerns over potential reactions, tended to seek information from their family and school, and appeared eager to be active participants in the decision-making process. Adolescents and males might be more likely to delay or refuse vaccines, which is supported by the fact that rates of HPV vaccination are lower than infant immunisation programs (90%) [48] with lower uptake in boys (66%) than girls (77%) [49]. Adding the science of vaccines and immunisation to the school curriculum could be a new approach to improve current vaccination coverage rates in adolescents and also enhance vaccine confidence in the next generation of parents. As our study identified vaccine safety as a concern and potential barrier, engaging adolescents early in understanding the scientific basis of benefits and risks associated with immunisation is more likely to improve confidence in decision making about maternal and infant immunisations in the future. Tailored school-based educational programs based on school specific sociodemographic factors should be developed to provide accurate information on the benefits and risks of vaccination and alleviate anxiety and concern.

Contributions

BW performed the data analyses and prepared the first draft of the manuscript under direct supervision of HM, LG and HH. LG and HH contributed to, reviewed and edited the manuscript. HM assisted in study design and contributed to, reviewed and edited the manuscript. MC, JR and GC assisted in study design and reviewed and edited the manuscript. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

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Conflict of interest

Associate Professor Helen Marshall has been a member of vaccine advisory boards for GlaxoSmithKline Biologicals and Wyeth, and has received travel support from CSL, Pfizer, Novartis, and GlaxoSmithKline Biologicals to present scientific data at international meetings. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, and Novartis Vaccines. Michelle Clarke has received a travel support grant from GlaxoSmithKline to present independent research at a national conference. There are no other conflicts of interest to declare.

Submission declaration and verification

All authors acknowledge that the article has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Trial registration site and number

This study has not been registered in a clinical trial registry because it was not a clinical trial and therefore registration was not required.

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References

[1] Anderson RM, May RM. Immunisation and herd immunity. Lancet 1990;335 (8690):641–5.
[2] Dube E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. Hum Vaccin Immunother 2013;9(8):1763–73.
[3] Hull BP, Dey A, Beard FH, Menzies RI, Brotherton JM, McIntyre PB. Immunisation coverage annual report, 2013. Commun Dis Intell Q Rep 2016;40(1):E146–69.
[4] Dorell C, Yankey D, Kennedy A, Stokley S. Factors that influence parental vaccination decisions for adolescents, 13 to 17 years old: National Immunization Survey-Teen, 2010. Clin Pediatr (Phila) 2013;52(2):162–70.
[5] Rand CM, Humiston SG, Schaffer SJ, Albertin CS, Shone LP, Blumkin AK, et al. Parent and adolescent perspectives about adolescent vaccine delivery: practical considerations for vaccine communication. Vaccine 2011;29 (44):7651–8.
[6] Rand CM, Schaffer SJ, Humiston SG, Albertin CS, Shone LP, Heintz EV, et al. Patient-provider communication and human papillomavirus vaccine acceptance. Clin Pediatr (Phila) 2011;50(2):106–13.
[7] Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991–2001. Vaccine 2005;23(48–49):5670–87.
[8] Larson HJ, Jarrett C, Eckersberger E, Smith DM, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. Vaccine 2014;32 (19):2150–9.
[9] Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. Pediatrics 2011;127(Suppl. 1):S92–9.
[10] Gust D, Brown C, Sheedy K, Hibbs B, Weaver D, Nowak G. Immunization attitudes and beliefs among parents: beyond a dichotomous perspective. Am J Health Behav 2005;29(1):81–92.
[11] Dempsey AF, Schaffer S, Singer D, Butchart A, Davis M, Freed GL. Alternative vaccination schedule preferences among parents of young children. Pediatrics 2011;128(5):848–56.
[12] Bedford H, Lansley M. More vaccines for children? Parents' views. Vaccine 2007;25(45):7818–23.
[13] Wang B, Clarke M, Afzali HH, Marshall H. Community, parental and adolescent awareness and knowledge of meningococcal disease. Vaccine 2014;32 (18):2042–9.
[14] Kennedy A, Stokley S, Curtis CR, Gust D. Limited awareness of vaccines recommended for adolescents and other results from two national consumer health surveys in the United States. J Adolesc Health 2012;50(2):198–200.
[15] Hessel L. Adolescent and vaccination: knowledge and perception. Ljubljana, Slovenia: VHPB; 2007.
[16] Balemans R, Devroey D, Van De Vijver E, Chovanova H, Vandevoorde J. Knowledge and attitudes about vaccinations among adolescents. J Prev Med Hyg 2011;52(2):64–72.
[17] Darden PM, Thompson DM, Roberts JR, Hale JJ, Pope C, Naifeh M, et al. Reasons for not vaccinating adolescents: National Immunization Survey of Teens, 2008–2010. Pediatrics 2013;131(4):645–51.
[18] Principi N, Esposito S. Adolescents and vaccines in the western world. Vaccine 2013;31(46):5366–74.
[19] Brabin L, Greenberg DP, Hessel L, Hyer R, Ivanoff B, Van Damme P. Current issues in adolescent immunization. Vaccine 2008;26(33):4120–34.
[20] Gowda C, Dong S, Potter RC, Dombkowski KJ, Dempsey AF. A population-level assessment of factors associated with uptake of adolescent-targeted vaccines in Michigan. J Adolesc Health 2013;53(4):498–505.

[21] Peretti-Watel P, Raude J, Sagaon-Teyssier L, Constant A, Verger P, Beck F. Attitudes toward vaccination and the H1N1 vaccine: poor people's unfounded fears or legitimate concerns of the elite? Soc Sci Med 2014;109:10–8.
[22] Marshall HS, Chen G, Clarke M, Ratcliffe J. Adolescent, parent and societal preferences and willingness to pay for meningococcal B vaccine: a Discrete Choice Experiment. Vaccine 2016;34(5):671–7.
[23] Freed GL, Clark SJ, Butchart AT, Singer DC, Davis MM. Parental vaccine safety concerns in 2009. Pediatrics 2010;125(4):654–9.
[24] Gust DA, Darling N, Kennedy A, Schwartz B. Parents with doubts about vaccines: which vaccines and reasons why. Pediatrics 2008;122(4):718–25.
[25] Lernout T, Theeten H, Hens N, Braeckman T, Roelants M, Hoppenbrouwers K, et al. Timeliness of infant vaccination and factors related with delay in Flanders, Belgium. Vaccine 2014;32(2):284–9.
[26] Vandermeulen C, Roelants M, Theeten H, Depoorter AM, Van Damme P, Hoppenbrouwers K. Vaccination coverage in 14-year-old adolescents: documentation, timeliness, and sociodemographic determinants. Pediatrics 2008;121(3):e428–34.
[27] Pink B. Information paper: an introduction to socio-economic indexes for areas (SEIFA), 2006. Canberra: Australian Bureau of Statistics (ABS); 2008.
[28] Larson HJ, Schulz WS, Tucker JD, Smith DM. Measuring vaccine confidence: introducing a global vaccine confidence index. PLoS Curr 2015:7.
[29] Gilkey MB, McRee AL, Brewer NT. Forgone vaccination during childhood and adolescence: findings of a statewide survey of parents. Prev Med 2013;56(3–4):202–6.
[30] Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? Pediatrics 2004;114(1):187–95.
[31] Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression. John Wiley & Sons; 2013.
[32] StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.
[33] Peretti-Watel P, Verger P, Raude J, Constant A, Gautier A, Jestin C, et al. Dramatic change in public attitudes towards vaccination during the 2009 influenza A(H1N1) pandemic in France. Eurosurveillance: bulletin europeen sur les maladies transmissibles = Eur Commun Disease Bull 2013;18(44).
[34] Gidengil CA, Parker AM, Zikmund-Fisher BJ. Trends in risk perceptions and vaccination intentions: a longitudinal study of the first year of the H1N1 pandemic. Am J Public Health 2012;102(4):672–9.
[35] Schwarzinger M, Flicoteaux R, Cortarenoda S, Obadia Y, Moatti JP. Low acceptability of A/H1N1 pandemic vaccination in French adult population: did public health policy fuel public dissonance? PLoS ONE 2010;5(4):e10199.
[36] Olofsson A, Rashid S. The white (male) effect and risk perception: can equality make a difference? Risk Anal 2011;31(6):1016–32.
[37] Nagata JM, Hernandez-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. Social determinants of health and seasonal influenza vaccination in adults >/=65 years: a systematic review of qualitative and quantitative data. BMC Pub Health 2013;13:388.
[38] Ndiritu M, Cowgill KD, Ismail A, Chiphatsi S, Kamau T, Fegan G, et al. Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new Haemophilus influenzae type b and hepatitis b virus antigens. BMC Pub Health 2006;6:132.
[39] Pavlopoulou ID, Michail KA, Samoli E, Tsiftis G, Tsoumakas K. Immunization coverage and predictive factors for complete and age-appropriate vaccination among preschoolers in Athens, Greece: a cross–sectional study. BMC Pub Health 2013;13:908.
[40] Goodenough B, Thomas W, Champion GD, Perrott D, Taplin JE, von Baeyer CL, et al. Unravelling age effects and sex differences in needle pain: ratings of sensory intensity and unpleasantness of venipuncture pain by children and their parents. Pain 1999;80(1–2):179–90.
[41] Unruh AM. Gender variations in clinical pain experience. Pain 1996;65(2–3):123–67.
[42] Cawley J, Hull HF, Rousculp MD. Strategies for implementing school-located influenza vaccination of children: a systematic literature review. J Sch Health 2010;80(4):167–75.
[43] Gowda C, Schaffer SE, Dombkowski KJ, Dempsey AF. Understanding attitudes toward adolescent vaccination and the decision-making dynamic among adolescents, parents and providers. BMC Pub Health 2012;12:509.
[44] Marshall HS, Proeve C, Collins J, Tooher R, O'Keefe M, Burgess T, et al. Eliciting youth and adult recommendations through citizens' juries to improve school based adolescent immunisation programs. Vaccine 2014;32(21):2434–40.
[45] Boshoff K, Dollman J, Magarey A. An investigation into the protective factors for overweight among low socio-economic status children. Health Promot J Austr 2007;18(2):135–42.
[46] Coad JE, Shaw KL. Is children's choice in health care rhetoric or reality? A scoping review. J Adv Nurs 2008;64(4):318–27.
[47] Windebank KP, Spinetta JJ. Do as I say or die: compliance in adolescents with cancer. Pediatr Blood Cancer 2008;50(S5):1099–100.
[48] ACIR – Current Data [Internet]. Department of Health and Ageing. Available from: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/acir-curr-data.htm> [cited 29 August 2016].
[49] National (Australia) HPV 3 dose vaccination coverage for adolescents turning 15 years of age [Internet]. Department of Health and Ageing. Available from: <http://www.hpvregister.org.au/research/coverage-data> [cited 29 August 2016].

2.3 VACCINE PREFERENCES

Adolescent vaccine preferences were evaluated in a national online survey and quantified by using a DCE design. The study results were published in “PLOS ONE”. The DCE online survey was completed by 800 adolescents. Most adolescents provided valid responses with an inconsistency rate of 13.1%. Attributes and levels were selected based on a literature review and expert opinions. Expert opinions were solicited from a clinician and researchers including three co-authors (HM, GC and BW) to develop attributes and attribute levels. The DCE data were analysed using mixed logit regression. Adolescents showed strong preferences for vaccination against a life-threatening illness with lower price, mild but common side effects, and delivery via a skin patch. Although adolescent school-based vaccination programs have been considered as an efficient and effective way to provide vaccines to this age group, the survey results showed that GP clinics were preferred by adolescents. Understanding drivers for vaccination in this population is key to designing effective public health programs. Previous work has only focused on particular vaccines rather than the broad approach to adolescent views taken in this study. This study has provided valuable insight into adolescent preferences for vaccination.

2.3.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Adolescent values for immunisation programs in Australia: A discrete choice experiment
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Principal Author

Name of Principal Author (Candidate)	Bing Wang		
Contribution to the Paper	BW conceived and designed the study, performed data analysis under instruction of GC and prepared the first draft of the manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Gang Chen		
Contribution to the Paper	GC instructed BW in data analysis, conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	11 October 2018

Name of Co-Author	Julie Ratcliffe		
Contribution to the Paper	JR assisted in study design, and contributed to, reviewed and edited the manuscript.		
Signature		Date	11/10/18

Name of Co-Author	Hossein Haji Ali Afzali		
Contribution to the Paper	HHAA contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/2018

Name of Co-Author	Lynne Giles		
Contribution to the Paper	LG contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/18

Name of Co-Author	Helen Marshall		
Contribution to the Paper	HM conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	04 OCT 2018

Please cut and paste additional co-author panels here as required.

2.3.2 PUBLICATION

PLOS ONE

RESEARCH ARTICLE

Adolescent values for immunisation programs in Australia: A discrete choice experiment

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Data Availability Statement: Data are from the ADVALUE study whose authors may be contacted at + 61 8 8161 8115. A minimal data set underlying the findings in our study has been uploaded in a supplemental file.

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Abstract

Objectives

The importance of adolescent engagement in health decisions and public health programs such as immunisation is becoming increasingly recognised. Understanding adolescent preferences and further identifying barriers and facilitators for immunisation acceptance is critical to the success of adolescent immunisation programs. This study applied a discrete choice experiment (DCE) to assess vaccination preferences in adolescents.

Methods

This study was conducted as a cross-sectional, national online survey in Australian adolescents. The DCE survey evaluated adolescent vaccination preferences. Six attributes were assessed including disease severity, target for protection, price, location of vaccination provision, potential side effects and vaccine delivery method. A mixed logit model was used to analyse DCE data.

Results

This survey was conducted between December 2014 and January 2015. Of 800 adolescents aged 15 to 19 years, stronger preferences were observed overall for: vaccination in the case of a life threatening illness ($p<0.001$), lower price vaccinations ($p<0.001$), mild but common side effects ($p = 0.004$), delivery via a skin patch ($p<0.001$) and being administered by a family practitioner ($p<0.001$). Participants suggested that they and their families would be willing to pay AU$394.28 (95%CI: AU$348.40 to AU$446.92) more for a vaccine targeting a life threatening illness than a mild-moderate illness, AU$37.94 (95%CI: AU$19.22 to AU$57.39) more for being vaccinated at a family practitioner clinic than a council immunisation clinic, AU$23.01 (95%CI: AU$7.12 to AU$39.24) more for common but mild and

Competing interests: Professor Helen Marshall is an independent investigator on clinical trials of investigational vaccines manufactured by pharmaceutical companies including GlaxoSmithKline, Novavax and Pfizer. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, and Pfizer Vaccines. There are no other conflicts of interest to declare. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Abbreviations: ACT, Australian Capital Territory; DCE, Discrete Choice Experiment; GP, General Practitioner; HPV, Human Papillomavirus–; NT, Northern Territory; SD, Standard Deviation; SEIFA IRSD, Socio-Economic Indexes for Areas,Index of Relative Socioeconomic Disadvantage; SES, Socio-Economic Status; STI, Sexually Transmitted Infection.

resolving side effects compared to rare but serious side effects, and AU$51.80 (95%CI: AU $30.42 to AU$73.70) more for delivery via a skin patch than injection.

Conclusions

Consideration of adolescent preferences may result in improved acceptance of, engagement in and uptake of immunisation programs targeted for this age group.

Introduction

Adolescence is a time in life that often features risk taking behaviours, however it also provides the greatest opportunity for sustained wellbeing into adulthood. Although adolescents are often treated as younger adults, their views and values are typically overlooked when public health strategies that affect them are being designed.

One of these strategies is immunisation, with adolescents an increasingly important target group for immunisation internationally [1]. Routine immunisation of adolescents provides individual protection and herd protection against vaccine-preventable diseases such as Human Papillomavirus (HPV) and meningococcal disease, boosts the pre-existing but waning immunity (e.g. diphtheria/tetanus/pertussis booster vaccination) and delivers catch-up programs for those who did not receive recommended vaccines during childhood [2]. However, compared to infant and childhood immunisation, the current adolescent immunisation coverage is suboptimal with uptake rates varying between 50% and 80% in high resource countries (e.g. Australia [3] and the United States [4]). Lack of awareness of vaccination recommendations, concerns about vaccine side effects, confusion over immunisation schedules and not actively attending preventive health visits could be barriers to vaccinating adolescents [5, 6]. However, earlier studies in this area have mainly focused on parental or adult preferences for immunisation or on a specific vaccine, such as for HPV, for adolescents [7–13]. Since there is an evidence base to indicate that adolescents are willing to be involved and their attitudes can significantly affect parents' vaccination decisions [5, 14, 15], adolescent immunisation uptake could be improved through better understanding adolescent preferences for vaccination. Understanding their preferences is also important for the development of any vaccination education programs. Such programs can overcome vaccine hesitancy or refusal, and can also provide vaccine providers and health authorities with useful information to inform policy prior to the introduction of any future targeted adolescent vaccine programs.

Discrete choice experiments (DCEs) are commonly used in health economics to elicit participants' preferences for healthcare programs and policies. The technique uses an attribute based quantitative survey method and draws on elements of random utility theory, consumer theory, and experimental design theory. In DCEs, a number of salient attributes are used to describe characteristics of interventions, and each attribute takes a range of levels. The value (utility) of each scenario is determined by different levels of attributes. Participants trade off risks and benefits among alternative scenarios and express their preferences by choosing their preferred option [16, 17]. Where price is included as an additional attribute, the DCE approach may also be used to estimate individuals' willingness to pay (WTP) for healthcare interventions [16]. Immunisation acceptance by adolescents may be influenced by a number of factors including severity of illness, side effects, out-of-pocket costs, healthcare facilities where vaccines are administered, mode of administration, vaccine effectiveness and duration

of immunity [9, 12]. Adolescents may choose to trade off the potential health benefits against perceived drawbacks of immunisation in the decision making dynamic.

An adolescent-friendly approach, which includes eliciting adolescent views on public health programs that we expect them to engage in, is required if we aim to reduce the barriers to taking part in such programs. Several different methodologies including DCEs have been used previously to assess adolescent values of health states [18, 19]. However, a limited amount of research has been conducted to date to assess adolescent preferences and attitudes towards immunisation program delivery [14, 20–22]. Using an online DCE, this study aimed to investigate adolescent preferences to determine the most important factors influencing their decisions for immunisation.

Methods

Survey development

This survey was conducted according to guidelines for the design and conduct of DCE studies in healthcare [17, 23–25].

For this study, it was important to identify a number of relevant and generic attributes that enable participants to make a meaningful judgment regarding adolescent preferences for immunisation. We considered a literature review and expert opinion (interview with a clinician in child and adolescent health and vaccinologist, a health economist/DCE expert, an ethicist and an adolescent health researcher) as the appropriate sources of information. A rapid systematic review was performed by searching titles and abstracts in the PubMed database for DCE studies investigating vaccines preferences. Experts were asked to review the list of attributes derived from the literature review, and the following were identified as appropriate to include in our DCE: disease target [26–29], location of vaccination [9, 13, 30, 31], potential for side effects [8–10, 13, 30–35], vaccine delivery mechanism [10] and price [9, 10, 13, 30, 31, 35, 36]. Since herd protection is an important factor affecting acceptance of vaccines and outcomes of cost-effectiveness evaluations [37], "target for protection" was also added to the attribute list based on the expert opinion. The levels of each attribute were selected as to whether they were plausible and relevant from both the clinical and the policy viewpoint. Based on the range of private vaccine prices in Australia (approximately AU$ 30–200 per dose) and assumption of at least three doses required, price levels of AU$100 and AU$500 were chosen in addition to publicly-funded free vaccination. A previous DCE study found the adolescents' personal financial situation was significantly associated with their vaccination choice rather than their household financial situation [7]. Considering some adolescents might have already worked full or part-time, we used the term "cost to self (or family)". Vaccine efficacy was selected as an attribute in a number of previous DCE studies [8–10, 13, 26–34], but not included in our DCE survey as it was not reported as a major contributor to vaccine hesitancy or refusal [38, 39]. Previous research found participants' decisions to vaccinate were not sensitive to the probability of disease [35]. Therefore neither disease prevalence nor incidence were included in order to reduce participants' cognitive burden.

A D-efficient (D_z-error, i.e. zero priors assumed for all variables) design, for main effects only, was developed using Ngene 1.1.2 [40], which yielded 36 choice sets that were further divided into three blocks so as to minimise participants' cognitive burden. Each participant was randomly assigned to one of the three blocks. One choice question in each block was repeated to check for internal consistency. An example of a choice question is shown in Table 1. Before participants were asked to make a choice between options A or B for each choice question, a detailed explanation of how to choose between alternatives was presented. The possible differences in each hypothetical scenario were listed: 1) disease targeted including

Table 1. Example of a DCE question. Please consider that you are making a choice about receiving a vaccine/s for yourself. Of the options in the table below (A or B), please select which option you would choose. Considering the possible scenarios outlined below, which option would you choose?

Features	Option A	Option B
Disease targeted	Chronic illness	Mild-moderate illness (unlikely to be fatal)
Target for protection	The individual (you)–being vaccinated will provide protection against disease affecting adolescents and young adults	The individual (you) and others–being vaccinated will protect the individual (you) and others by reducing spread of disease to others in the community
Cost to self (or family)	$500	$100
Location of vaccination	General practitioner (GP)	School/University
Potential for side effects	Common but mild and resolving (i.e. fever, local redness or swelling)	Rare (1:100,000) but serious (i.e. allergic reaction)
Vaccine delivery mechanism	Oral dose	Skin patch
Which option would you be more likely to choose?	○	○

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mild-moderate illness (unlikely to be fatal), life threatening illness (could be fatal), sexually transmitted infection, or chronic illness; 2) target for protection including the individual (you)–being vaccinated will provide protection against disease affecting adolescents and young adults, or the individual (you) and others–being vaccinated will protect the individual (you) and others by reducing spread of disease to others in the community; 3) price including $0, $100, or $500; 4) setting (location of vaccination) including school/university, GP (i.e. family practitioner), or council immunisation clinic; 5) potential for side effects including rare (1:100,000) but serious (i.e. allergic reaction), or common but mild and resolving (i.e. fever, local redness or swelling); 6) vaccine delivery mechanism including injection (needle), skin patch, or oral dose.

The questionnaire included a series of socio-demographic questions and 13 DCE choice questions. In addition, two questions in relation to attitudes towards risk in general or with health were measured on an eleven point scale, with zero indicating "not at all prepared to take risk", and ten indicating "very much prepared to take risk" [41] to assess risk taking behaviours.

The draft survey questionnaire was pre-piloted with a convenience sample of three adolescents and only minor changes were made to ensure adolescents could interpret all questions appropriately. The survey was also pilot tested in 130 participants with approximately 43 participants per block to check feasibility and internal consistency. Seventeen participants (13.1%) failed the internal consistency test. Since the inconsistency rate was comparable to that reported in previous DCE studies [42, 43], no revisions were made to the DCE survey.

Sample size and study population

Calculation of optimal sample sizes is complex as it depends on the true values of the unknown parameters estimated in the DCE models [17]. However, as a rule of thumb suggested by Orme [44], a sample size of 300 would be desirable for a main effects model based on the number of choice sets, alternatives and analysis cells. We aimed to recruit 20 participants per choice set resulting in 720 adolescents aged between 15–19 years, which would provide more

statistical power with a sample size larger than in similar adolescent DCE studies described in the literature to date [7, 8, 32].

Potential participants were identified via Pureprofile (https://www.pureprofile.com/au/), an online market research company. Pureprofile was contracted to host and distribute the survey invitation to parents on their database who had children aged between 15–19 years and resided within Australia. Interested parents were provided with an electronic information sheet describing the study. Parents were then asked whether they had an adolescent who would be willing to complete the survey. Subsequent to parent and adolescent dyad consent to participate in the study, adolescents were then guided through the online survey by screen prompts. In recognition of the time spent completing the DCE survey, account holders of adolescents who participated received a small financial reward (AU$3.25).

Statistical analysis

The Socio-Economic Indexes for Areas, Index of Relative Socioeconomic Disadvantage 2011 (SEIFA IRSD) [45] was used to categorise socio-economic status as into tertiles: low (1st–33rd percentile), medium (34th–66th percentile) and high (67th–100th percentile). SEIFA ranks residential areas in Australia according to relative socio-economic disadvantage based on information from the five-yearly Census. Student's t-tests and χ^2 tests were used to compare means and proportions between two subgroups, respectively. Participants who failed the internal consistency test were excluded from the analysis and a sensitivity analysis was conducted by including participants who failed the test.

DCE data were analysed using a mixed-logit model which accounts for preference heterogeneity. The price attribute was treated as a continuous variable and dummy-variable coding was used for all other attributes. The model fit to the utility function was:

$$\begin{aligned} U_{itj} = \quad & (\beta 1 + \eta_{1i})\ \text{life threatening illness} + (\beta 2 + \eta_{2i})\ \text{sexually transmitted infection} \\ & + (\beta 3 + \eta_{3i})\ \text{chronic illness} + (\beta 4 + \eta_{4i})\ \text{protect you \& others} \\ & + (\beta 5 + \eta_{5i})\ \text{school/university} + (\beta 6 + \eta_{6i})\ \text{GP} + (\beta 7 + \eta_{7i})\ \text{common side effects} \\ & + (\beta 8 + \eta_{8i})\ \text{skin patch} + (\beta 9 + \eta_{9i})\ \text{oral dose} + (\beta 10 + \eta_{10i})\ \text{price} + \varepsilon_{itj} \end{aligned}$$

U_{itj} describes the utility of a hypothetical vaccine scenario, i derives from an individual choosing alternative j in choice question t, β_i is a vector of coefficients reflecting participants' preference for each attribute level on average, η_i indicates the individual's specific preference (i.e. a random effect), and ε_{itj} is a random error term describing the unmeasured variation in participants' preferences. We assumed coefficients of all attribute levels were independent and randomly distributed with a Normal distribution. A positive (negative) and significant coefficient indicates a positive (negative) preference for a specific attribute level. The coefficient estimates (or preference weights) can also be used to compare relative importance between different levels of the same attribute or between levels of completely different attributes [11].

WTP represents a monetary measure of participants' valuation for a change in the level of the attribute of interest. It is the ratio of the coefficient for a certain attribute and the price coefficient ($-\frac{\beta_k}{\beta_c}$ where $\beta_c$is the price coefficient and $\beta_k$is the coefficient for attribute k). The positive and negative results indicate theoretically to what extent the participants and their families would be willing to pay/to be compensated for an attribute level. The 95% confidence intervals were estimated using the Krinsky Robb (parametric bootstrap) method [46]. WTP estimates do not represent market prices participants and their families wanted to pay for the various attributes of a hypothetical vaccine. All statistical analyses were performed in Stata version 14.1 [47].

Ethics

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee in Adelaide, Australia. This study has not been registered in a clinical trial registry because it was not a clinical trial and therefore registration was not required.

Results

A total of 800 adolescents (age range 15–19 years) were enrolled and completed the survey between December 2014 and January 2015 (S1 Dataset). Females were slightly predominant (54.9%) in the study population. Of the participants, 90.0% were born in Australia, with approximately 97.8% non-indigenous (Table 2). Enrolment was initially planned to be stratified by state and gender. Due to difficulties in recruiting adolescent participants in smaller states or territories such as the Northern Territory (NT) and Australian Capital Territory (ACT), enrolment did not strictly adhere to the original regional quotas. Except for NT and ACT, participants were reasonably representative of the adolescent population of each state.

DCE results

Participants who failed the consistency test were excluded from the analysis (N = 105, 13.1%), generating a useable total sample of 695 adolescents (86.9%) for main DCE analysis. Except for socio-economic status (SES) and risk taking attitudes, there were no significant differences between the participants who passed versus those who failed the consistency test. Those who were excluded were more likely to reside in an area with medium SES ($p = 0.008$) and exhibited higher general ($p = 0.015$) and health risk attitudes ($p = 0.004$).

The vaccination in the case of a life threatening illness ($p<0.001$) had the highest preference weight when comparing with a mild-moderate illness (Fig 1 and Table 3). Changing vaccination targeting from a mild-moderate illness to a life threatening illness could yield 17 times ($2.314 \div 0.135$) as much as utility as changing from "rare but serious" to "common but mild and resolving" side effects. Other stronger preferences were observed for vaccination treating a chronic illness ($p<0.001$) and a sexually transmitted infection ($p<0.001$) with common but mild and resolving side effects ($p = 0.004$) and delivery via a skin patch or oral dose ($p<0.001$) compared with their reference levels. Despite the success of adolescent school-based vaccination, participants were more willing to be vaccinated by GPs ($p<0.001$). Lower price vaccinations were also preferred ($p<0.001$).

With the exception of one coefficient (for vaccination protecting you and others ($p = 0.274$)), the standard deviations (SDs) of other random coefficients were statistically significant, which indicated preference heterogeneity was present for those attribute levels.

A sensitivity analysis was performed by including participants who failed the consistency test and no significant impact was observed. Subgroup analyses were conducted with regard to SES, risk taking attitudes and participants' intention to be vaccinated, and the results were broadly consistent between subgroups.

Willingness to pay

Participants suggested that they and their families would be willing to pay AU$394.28 (95%CI: AU$348.40 to AU$446.92) more for a vaccine targeting a life threatening illness than a mild-moderate illness, AU$37.94 (95%CI: AU$19.22 to AU$57.39) more for being vaccinated at a family practitioner clinic than a council immunisation clinic, AU$23.01 (95%CI: AU$7.12 to AU$39.24) more for common but mild and resolving side effects than rare but serious side

Table 2. Demographic characteristics of the study population.

	All (N = 800)		Participants who passed the consistency test only (N = 695)		Participants who failed the consistency test only (N = 105)		P value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	17.10	1.42	17.11	1.42	17.08	1.39	0.839
Household Size (people)	4.09	1.41	4.05	1.35	4.30	1.77	0.088
Risk attitudes							
In general	5.20	2.32	5.12	2.26	5.71	2.64	0.015
For health	4.11	2.61	4.01	2.53	4.79	3.00	0.004
	N	%	N	%	N	%	
Gender							
Male	361	45.13	317	45.61	44	41.90	0.477
Female	439	54.88	378	54.39	61	58.10	
Completed High School	445	55.63	391	56.26	54	51.43	0.353
Born in Australia	720	90.00	629	90.50	91	86.67	0.222
Aboriginal or Torres Strait Islander	17	2.13	16	2.30	1	0.95	0.371
Socio-economic Status							
Low (1st–33rd percentile)	203	25.50	183	26.48	20	19.05	0.008
Medium (34th–66th percentile)	252	31.66	205	29.67	47	44.76	
High (67th–100th percentile)	341	42.84	303	43.85	38	36.19	
State							
NSW	257	32.13	224	32.23	33	31.43	0.224
VIC	201	25.13	173	24.89	28	26.67	
QLD	166	20.75	149	21.44	17	16.19	
SA	70	8.75	55	7.91	15	14.29	
WA	79	9.88	68	9.78	11	10.48	
TAS	16	2.00	16	2.30	0	0.00	
ACT & NT	11	1.38	10	1.44	1	0.95	

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effects, and AU$51.80 (95%CI: AU$30.42 to AU$73.70) more for delivery via a skin patch than injection (Table 4).

Discussion

This DCE has identified preferences of Australian adolescents for immunisations providing protection against a life threatening illness, causing common but mild and resolving side effects, being administered by a medical practitioner and delivered via a skin patch at a lower price. To our knowledge this is the first study to investigate adolescent preferences for immunisation delivery using a DCE design. Because comparable data are lacking, we have reviewed literature for DCE studies associated with a specific vaccine in both parental and adolescent populations.

Fatal diseases were the most vital decisive factor in adolescent vaccine acceptance. Another DCE study reported people valued prevention targeting a serious illness higher than cure [48]. This suggests that vaccines targeted towards a fatal illness could achieve high and sustainable vaccine coverage, for example, adolescent vaccines for meningococcal disease. Given the National HPV Vaccination Program started almost ten years ago [49], somewhat surprisingly, our study participants were not strongly in favour of STI vaccines which may indicate lack of awareness of HPV being a STI. Parental studies reported similar results that a sexual mode of transmission had minimal impact on STI vaccine acceptability [27, 28]. Moreover, only 13% of

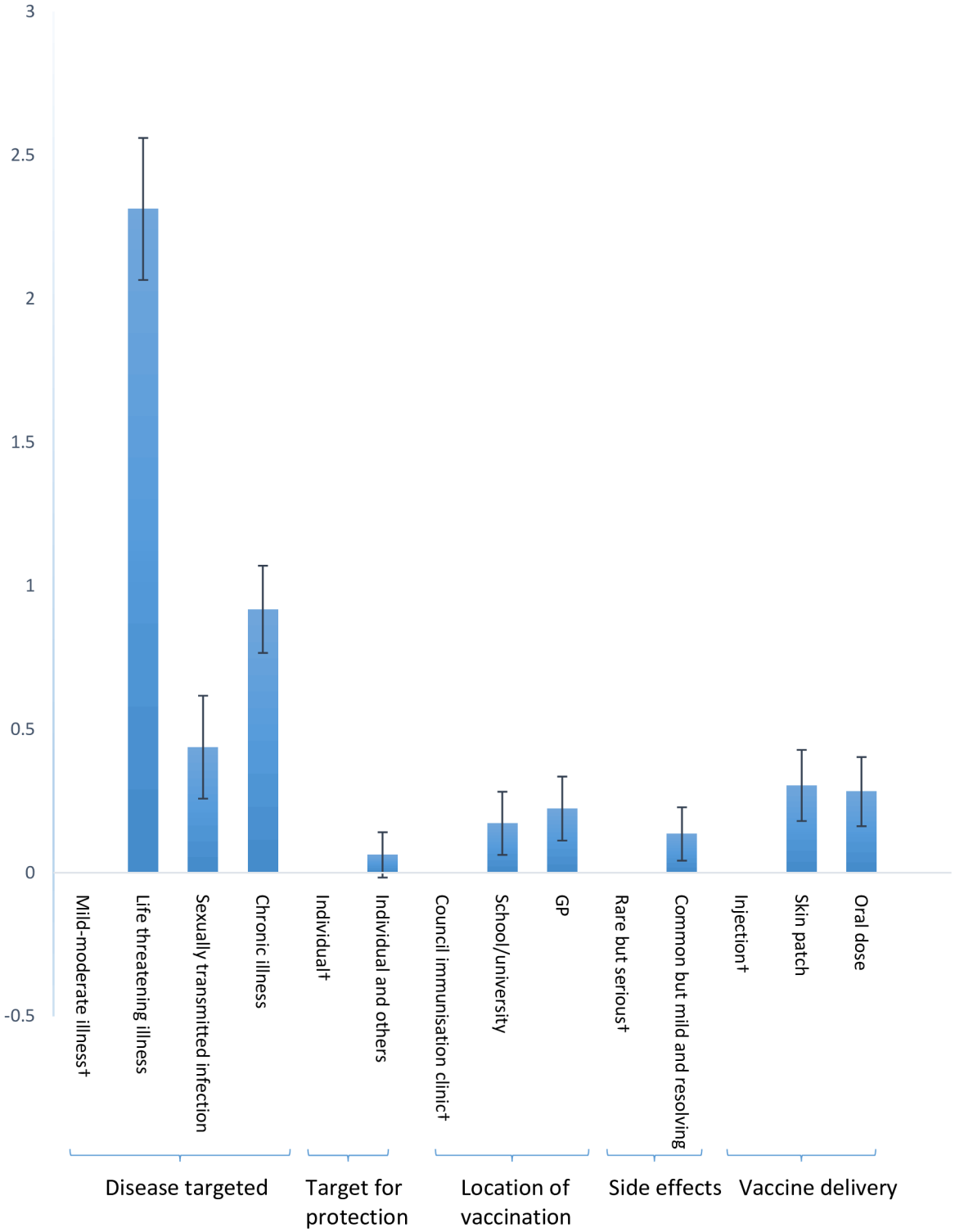

Fig 1. Preference weights for nonmonetary attributes. † Reference (omitted) level for each attribute.

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Table 3. Mixed logit estimates on vaccination preferences.

Attributes	Coefficient	SE	P value	SD	SE	P value
Disease targeted						
Mild-moderate illness [a]						
Life threatening illness	2.314	0.126	<0.001	1.909	0.135	<0.001
Sexually transmitted infection	0.437	0.092	<0.001	1.408	0.101	<0.001
Chronic illness	0.918	0.078	<0.001	0.418	0.178	0.019
Target for protection						
Individual [a]						
Individual and others	0.062	0.040	0.126	0.113	0.103	0.274
Location of vaccination						
Council immunisation clinic [a]						
School/university	0.172	0.056	0.002	0.267	0.125	0.033
GP	0.223	0.057	<0.001	0.290	0.120	0.016
Potential for side effects						
Rare but serious [a]						
Common but mild and resolving	0.135	0.047	0.004	0.558	0.067	<0.001
Vaccine delivery mechanism						
Injection [a]						
Skin patch	0.304	0.063	<0.001	0.566	0.091	<0.001
Oral dose	0.283	0.062	<0.001	0.302	0.127	0.018
Price	-0.006	<0.001	<0.001	0.006	<0.001	<0.001
Log likelihood	-3893.719					
Number of participants [b]	695					
Number of observations [c]	16680					

Notes: SE—standard errors. SD—standard deviation. For all random coefficients, normal distribution was used. Price attribute was included as a continuous variable; all other attributes were dummy coded.

[a] Reference (omitted) level for each attribute

[b] A total of 800 adolescents completed the survey. Participants who failed the consistency test (N = 105) were excluded from the main analysis reported in this table.

[c] In total, 16680 scenarios (2*12*695) were assessed, with 12 choice sets per participant and each consisting of a choice between two alternative vaccination programs (A and B).

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adolescent girls were concerned about HPV in an HPV study conducted in the United States [7]. Perceived transmission risks or severity of STI might be quite low in adolescents, which resulted in a relatively lower estimated coefficient on STI compared to life threatening and chronic illnesses. Although previous research indicated participants' choices to vaccinate were not sensitive to the probability of disease [35], assumptions made by participants about the incidence of the disease prevented might influence their preferences. The results of disease severity may be interpreted with caution, for example, we cannot definitively conclude that adolescents indicated they and their families would be willing to pay AU$394 more for a vaccine against a life-threatening but potentially very rare disease, as compared with a mild-moderate, but common one. Further research may be warranted to tease out the effects of the disease incidence versus disease severity.

Adolescent immunisation preferences were also influenced by the severity of potential side effects. Previous research only assessed impact of the frequency of severe reactions [9, 30, 33, 34]. Our study compared preferences between two common occurrences of side effects: rare

Table 4. Willingness to pay (AU$) for vaccination (based on mixed logit estimates).

Attributes	Willingness to pay (AU$)	95%CI
Disease targeted		
Mild-moderate illness [a]		
Life threatening illness	394.28	348.40, 446.92
Sexually transmitted infection	74.43	44.10, 106.37
Chronic illness	156.35	129.76, 185.55
Target for protection		
Individual [a]		
Individual and others	10.53	-3.29, 24.52
Location of vaccination		
Council immunisation clinic [a]		
School/university	29.33	10.70, 48.54
GP	37.94	19.22, 57.39
Potential for side effects		
Rare but serious [a]		
Common but mild and resolving	23.01	7.12, 39.24
Vaccine delivery mechanism		
Injection [a]		
Skin patch	51.80	30.42, 73.70
Oral dose	48.25	27.95, 69.82
Number of observations	16680	

Notes: Confidence interval (CI) was calculated based on the Krinsky and Robb bootstrap method (with 10,000 replications). Price attribute was included as a continuous variable; all other attributes were dummy coded.

[a] Reference (omitted) level for each attribute.

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but serious versus common but mild. Compared to the frequency, the severity of side effects may play a more important role in the decision making process.

Although participants still showed positive preferences for the school or university, GP clinics were their stronger location preference in our study. In Australia, adolescent school-based vaccination has demonstrated advantages over community or private sectors and achieved a higher coverage rate [1]. However, a lack of awareness or miscommunication might affect their preference for school-based vaccination. More chances to communicate with GPs and understanding benefits and risks of the vaccination might explain why participants preferred GP clinics in our study. Similar to our finding, a varicella vaccination study reported that the provision of vaccination at schools did not affect parents' choices whether or not to immunise their child [31].

Our study also found that price was an important attribute driving preferences which is in line with previous research [9, 11, 31, 50, 51]. Recommended but non-publicly funded vaccines were more likely to be refused by parents due to the price [50]. If a vaccine was not included on the National Immunisation Program Schedule, vaccine prices would definitely be a financial barrier to successful implementation of an immunisation program. Although adolescents usually would not have any income or direct out-of-pocket costs for their medical care, a DCE study assessing WTP for a meningococcal B vaccine in Australia found a consistent pattern of results at all attributes and levels between adolescents and adults [12]. That financial barrier would still affect adolescent actual decision making when it comes to receipt of vaccines.

The strength of this study is identification of adolescent preferences for immunisation programs using a DCE survey, which allows us to investigate multiple factors influencing vaccination decision and trade-off between attribute levels. Based on a large national sample of adolescents, our study produced meaningful and robust estimates. There were some limitations to our study. Prior qualitative work was not conducted to select attributes and levels. It is possible that some potentially important attributes were omitted from the design of this study (e.g. disease incidence). Since preferences were measured to establish which components define the most preferred vaccine program from an adolescent perspective, an opt-out option was not provided and participants were forced to choose between two alternatives. Whilst it may be argued that including an opt-out option might reflect the decisions of participants in real-life settings, the opt-out option might be selected by participants to avoid making difficult trade-offs on attribute levels, thereby decreasing the precision of parameter estimates [52]. However, the inclusion of an opt-out option may provide more information about trade-offs between vaccination and no vaccination. Furthermore the opt-out option would have enabled the prediction of probabilities of take-up of different vaccine scenarios [17, 31] and might correct the WTP value for the probability of people opting out [53]. Further research is required to explore the implications of including an opt-out option in this context. Their identification and vaccination status cannot be verified, which may affect internal validity of the study. As our participants were adolescents who might not be financially independent, the WTP values in our study are a mix of personal values and perception of what their family would sacrifice and therefore WTP may not be interpreted in the conventional way. Finally, since this is a survey-research study and only participants with internet access could be enrolled, the sample may not be entirely representative of the general population of adolescents due to a higher percentage of adolescents from areas of high/medium SES with higher educational levels.

Understanding barriers and facilitators to immunisation is an important step to improve the uptake of adolescent immunisation. Our study showed adolescents' vaccine decisions were driven by disease types, healthcare facilities where vaccines were administered, severity of side effects and vaccine delivery methods. The study results can provide useful information on adolescent views, values and preferences for vaccination to health authorities, vaccine providers, immunisation educators and healthcare providers. Strategies to increase immunisation uptake among adolescents may include providing adolescent-tailored education programs, lowering out-of-pocket costs, and offering vaccinations outside of schools in "complementary" settings (e.g. GP clinics). This study evaluating adolescent preferences for immunisation may be used to inform any future health economic studies for individual vaccines before they are publicly available. For example, the predicted high rates of vaccination against fatal illnesses, may positively affect outcomes of health economic evaluation. Our study results may also be used to develop adolescent specific immunisation education programs. When designing an education program for adolescent immunisation, these factors, particularly the relative severity of the disease, should be clearly explained to adolescents.

Supporting information

S1 Dataset. DCE data from participants in this study.
(XLSX)

Author Contributions

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References

1. Ward K, Quinn H, Bachelor M, Bryant V, Campbell-Lloyd S, Newbound A, et al. Adolescent school-based vaccination in Australia. Commun Dis Intell Q Rep. 2013; 37(2):E156–67. PMID: 24168090
2. World Health Organization. Summary of WHO position papers—recommendations for routine immunization. Immunization VAB, 2014.
3. National Human Papillomavirus Vaccination Program Register. HPV Vaccination Coverage 2015. http://www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-2015. Access 15 June, 2016.
4. Centers for Disease Control and Prevention. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years—United States, 2015. https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a4.htm. Access 28 October, 2016
5. Gowda C, Schaffer SE, Dombkowski KJ, Dempsey AF. Understanding attitudes toward adolescent vaccination and the decision-making dynamic among adolescents, parents and providers. BMC Public Health. 2012; 12:509. https://doi.org/10.1186/1471-2458-12-509 PMID: 22768870
6. Oster NV, McPhillips-Tangum CA, Averhoff F, Howell K. Barriers to adolescent immunization: a survey of family physicians and pediatricians. J Am Board Fam Med. 2005; 18(1):13–9.
7. Brown DS, Poulos C, Johnson FR, Chamiec-Case L, Messonnier ML. Adolescent girls' preferences for HPV vaccines: a discrete choice experiment. Adv Health Econ Health Serv Res. 2014; 24:93–121. PMID: 25244906
8. de Bekker-Grob EW, Hofman R, Donkers B, van Ballegooijen M, Helmerhorst TJ, Raat H, et al. Girls' preferences for HPV vaccination: a discrete choice experiment. Vaccine. 2010; 28(41):6692–7. https://doi.org/10.1016/j.vaccine.2010.08.001 PMID: 20708696
9. Veldwijk J, Lambooij MS, Bruijning-Verhagen PC, Smit HA, de Wit GA. Parental preferences for rotavirus vaccination in young children: a discrete choice experiment. Vaccine. 2014; 32(47):6277–83. https://doi.org/10.1016/j.vaccine.2014.09.004 PMID: 25236585
10. Shono A, Kondo M. Parents' preferences for seasonal influenza vaccine for their children in Japan. Vaccine. 2014; 32(39):5071–6. https://doi.org/10.1016/j.vaccine.2014.07.002 PMID: 25063570
11. Poulos C, Reed Johnson F, Krishnarajah G, Anonychuk A, Misurski D. Pediatricians' preferences for infant meningococcal vaccination. Value Health. 2015; 18(1):67–77. https://doi.org/10.1016/j.jval.2014.10.010 PMID: 25595236
12. Marshall HS, Chen G, Clarke M, Ratcliffe J. Adolescent, parent and societal preferences and willingness to pay for meningococcal B vaccine: A Discrete Choice Experiment. Vaccine. 2016; 34(5):671–7. https://doi.org/10.1016/j.vaccine.2015.11.075 PMID: 26740249
13. Cameron MP, Newman PA, Roungprakhon S, Scarpa R. The marginal willingness-to-pay for attributes of a hypothetical HIV vaccine. Vaccine. 2013; 31(36):3712–7. https://doi.org/10.1016/j.vaccine.2013.05.089 PMID: 23747452
14. Rand CM, Humiston SG, Schaffer SJ, Albertin CS, Shone LP, Blumkin AK, et al. Parent and adolescent perspectives about adolescent vaccine delivery: practical considerations for vaccine communication. Vaccine. 2011; 29(44):7651–8. https://doi.org/10.1016/j.vaccine.2011.08.002 PMID: 21839793
15. Rand CM, Schaffer SJ, Humiston SG, Albertin CS, Shone LP, Heintz EV, et al. Patient-provider communication and human papillomavirus vaccine acceptance. Clin Pediatr (Phila). 2011; 50(2):106–13.
16. Ryan M, Gerard K, Amaya-Amaya M. Using discrete choice experiments to value health and health care: Springer Science & Business Media; 2007.

17. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics. 2008; 26(8):661–77. PMID: 18620460

18. Ratcliffe J, Flynn T, Terlich F, Stevens K, Brazier J, Sawyer M. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the Child Health Utility 9D. Pharmacoeconomics. 2012; 30(8):713–27. https://doi.org/10.2165/11597900-000000000-00000 PMID: 22788261

19. Ratcliffe J, Stevens K, Flynn T, Brazier J, Sawyer MG. Whose values in health? An empirical comparison of the application of adolescent and adult values for the CHU-9D and AQOL-6D in the Australian adolescent general population. Value Health. 2012; 15(5):730–6. https://doi.org/10.1016/j.jval.2012.04.005 PMID: 22867783

20. Balemans R, Devroey D, Van De Vijver E, Chovanova H, Vandevoorde J. Knowledge and attitudes about vaccinations among adolescents. J Prev Med Hyg. 2011; 52(2):64–72. PMID: 21842708

21. Kennedy A, Stokley S, Curtis CR, Gust D. Limited awareness of vaccines recommended for adolescents and other results from two national consumer health surveys in the United States. J Adolesc Health. 2012; 50(2):198–200. https://doi.org/10.1016/j.jadohealth.2011.04.017 PMID: 22265117

22. Wang B, Clarke M, Afzali HH, Marshall H. Community, parental and adolescent awareness and knowledge of meningococcal disease. Vaccine. 2014; 32(18):2042–9. https://doi.org/10.1016/j.vaccine.2014.02.054 PMID: 24593997

23. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. 2011; 14(4):403–13. https://doi.org/10.1016/j.jval.2010.11.013 PMID: 21669364

24. Hauber AB, Gonzalez JM, Groothuis-Oudshoorn CG, Prior T, Marshall DA, Cunningham C, et al. Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force. Value Health. 2016;19(4):300–15.

25. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health. 2013;16(1):3–13.

26. Determann D, Korfage IJ, Lambooij MS, Bliemer M, Richardus JH, Steyerberg EW, et al. Acceptance of vaccinations in pandemic outbreaks: a discrete choice experiment. PLoS One. 2014; 9(7):e102505. https://doi.org/10.1371/journal.pone.0102505 PMID: 25057914

27. Stockwell MS, Rosenthal SL, Sturm LA, Mays RM, Bair RM, Zimet GD. The effects of vaccine characteristics on adult women's attitudes about vaccination: a conjoint analysis study. Vaccine. 2011; 29(27):4507–11. https://doi.org/10.1016/j.vaccine.2011.04.031 PMID: 21527303

28. Zimet GD, Mays RM, Sturm LA, Ravert AA, Perkins SM, Juliar BE. Parental attitudes about sexually transmitted infection vaccination for their adolescent children. Arch Pediatr Adolesc Med. 2005; 159(2):132–7. https://doi.org/10.1001/archpedi.159.2.132 PMID: 15699306

29. Bair RM, Mays RM, Sturm LA, Perkins SM, Juliar BE, Zimet GD. Acceptability to Latino parents of sexually transmitted infection vaccination. Ambul Pediatr. 2008; 8(2):98–103. https://doi.org/10.1016/j.ambp.2007.11.002 PMID: 18355738

30. Veldwijk J, van der Heide I, Rademakers J, Schuit AJ, de Wit GA, Uiters E, et al. Preferences for Vaccination: Does Health Literacy Make a Difference? Med Decis Making. 2015; 35(8):948–58. https://doi.org/10.1177/0272989X15597225 PMID: 26338176

31. Hall J, Kenny P, King M, Louviere J, Viney R, Yeoh A. Using stated preference discrete choice modelling to evaluate the introduction of varicella vaccination. Health Econ. 2002; 11(5):457–65. https://doi.org/10.1002/hec.694 PMID: 12112494

32. Hofman R, de Bekker-Grob EW, Richardus JH, de Koning HJ, van Ballegooijen M, Korfage IJ. Have preferences of girls changed almost 3 years after the much debated start of the HPV vaccination program in The Netherlands? A discrete choice experiment. PLoS One. 2014; 9(8):e104772. https://doi.org/10.1371/journal.pone.0104772 PMID: 25136919

33. Arbiol J, Yabe M, Nomura H, Borja M, Gloriani N, Yoshida S. Using discrete choice modeling to evaluate the preferences and willingness to pay for leptospirosis vaccine. Hum Vaccin Immunother. 2015; 11(4):1046–56. https://doi.org/10.1080/21645515.2015.1010901 PMID: 25764105

34. Hofman R, de Bekker-Grob EW, Raat H, Helmerhorst TJ, van Ballegooijen M, Korfage IJ. Parents' preferences for vaccinating daughters against human papillomavirus in the Netherlands: a discrete choice experiment. BMC Public Health. 2014; 14:454. https://doi.org/10.1186/1471-2458-14-454 PMID: 24885861

35. Sadique MZ, Devlin N, Edmunds WJ, Parkin D. The effect of perceived risks on the demand for vaccination: results from a discrete choice experiment. PLoS One. 2013; 8(2):e54149. https://doi.org/10.1371/journal.pone.0054149 PMID: 23408936

36. Gidengil C, Lieu TA, Payne K, Rusinak D, Messonnier M, Prosser LA. Parental and societal values for the risks and benefits of childhood combination vaccines. Vaccine. 2012; 30(23):3445–52. https://doi.org/10.1016/j.vaccine.2012.03.022 PMID: 22449423

37. Holubar M, Stavroulakis MC, Maldonado Y, Ioannidis JP, Contopoulos-Ioannidis D. Impact of vaccine herd-protection effects in cost-effectiveness analyses of childhood vaccinations. A quantitative comparative analysis. PLOS ONE. 2017; 12(3):e0172414. https://doi.org/10.1371/journal.pone.0172414 PMID: 28249046

38. Dube E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. Hum Vaccin Immunother. 2013; 9(8):1763–73. https://doi.org/10.4161/hv.24657 PMID: 23584253

39. Gilkey MB, McRee AL, Brewer NT. Forgone vaccination during childhood and adolescence: findings of a statewide survey of parents. Prev Med. 2013; 56(3–4):202–6. https://doi.org/10.1016/j.ypmed.2012.12.019 PMID: 23295175

40. ChoiceMetrics. Ngene 1.1.2 User Manual & Reference Guide. Sydney, Australia: ChoiceMetrics; 2014.

41. Dohmen T. Individual risk attitudes new evidence from a large, representative, experimentally-validated survey. Bonn, Germany: IZA; 2005. http://www.iza.org/en/webcontent/publications/papers/viewAbstract?dp_id=1730. Accessed 15 June 2016

42. Hiligsmann M, Dellaert BG, Dirksen CD, van der Weijden T, Goemaere S, Reginster JY, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. Arthritis Res Ther. 2014; 16(1):R36. https://doi.org/10.1186/ar4465 PMID: 24479410

43. Wijnen BF, de Kinderen RJ, Colon AJ, Dirksen CD, Essers BA, Hiligsmann M, et al. Eliciting patients' preferences for epilepsy diagnostics: a discrete choice experiment. Epilepsy Behav. 2014; 31:102–9. https://doi.org/10.1016/j.yebeh.2013.11.029 PMID: 24389020

44. Orme B. Sample size issues for conjoint analysis studies. Sawthooth Software Research paper Series Squim, WA, USA: Sawthooth Software Inc. 1998.

45. Pink B. Socio-Economic Indexes for Areas (SEIFA) 2011. Canberra: Australian Bureau of Statistics. 2013.

46. Hole AR. A comparison of approaches to estimating confidence intervals for willingness to pay measures. Health Econ. 2007; 16(8):827–40. https://doi.org/10.1002/hec.1197 PMID: 17238222

47. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.

48. Luyten J, Kessels R, Goos P, Beutels P. Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment. Value Health. 2015; 18(2):224–33. https://doi.org/10.1016/j.jval.2014.12.007 PMID: 25773558

49. Australian Institute of Health. Australia's Health 2012: AIHW; 2012.

50. Marshall H, Ryan P, Roberton D, Beilby J. Varicella immunisation practice: Implications for provision of a recommended, non-funded vaccine. J Paediatr Child Health. 2009; 45(5):297–303. https://doi.org/10.1111/j.1440-1754.2009.01494.x PMID: 19493123

51. Ngorsuraches S, Nawanukool K, Petcharamanee K, Poopantrakool U. Parents' preferences and willingness-to-pay for human papilloma virus vaccines in Thailand. J Pharm Policy Pract. 2015; 8(1):20. https://doi.org/10.1186/s40545-015-0040-8 PMID: 26199734

52. Veldwijk J, Lambooij MS, de Bekker-Grob EW, Smit HA, de Wit GA. The effect of including an opt-out option in discrete choice experiments. PLoS One. 2014; 9(11):e111805. https://doi.org/10.1371/journal.pone.0111805 PMID: 25365169

53. Dhar R, Simonson I. The effect of forced choice on choice. J Mark Res. 2003; 40(2):146–60.

2.4 SUMMARY

The online surveys provided satisfactory answers to two research questions. Adolescent attitudes about vaccination differed from those of adults. Adolescents demonstrated a higher level of vaccine hesitancy with lower confidence and higher concerns about vaccination. They preferred vaccines against a life-threatening illness with a low price, mild but common side effects, delivery via a skin patch and be administered by a family practitioner. IMD is one of life-threatening diseases which is associated with high mortality and morbidity rates [18,19]. Since adolescents showed strong preferences for vaccination against a life-threatening illness, IMD is chosen to be further investigated as a case study. Five serogroups A, B, C, W and Y cause most meningococcal cases in the world. Serogroup B is one of the predominant serogroups. There has also been a rapid increase in the number of meningococcal serogroup W cases globally [31]. The vaccine for group B disease has not been included on the NIP due to failure to meet cost-effectiveness criteria in Australia [36]. New MenACWY vaccine programs have been included or are being considered to add on national immunisation schedules in a few countries [78]. In the next chapter, the burden of IMD and development of meningococcal vaccines have been thoroughly evaluated and reviewed. The implication of evaluating the burden of the disease and its vaccine development is profound, as this can provide solid evidence to inform future cost-effectiveness evaluations, support government funding decisions, and improve vaccine acceptance for new meningococcal vaccine programs.

CHAPTER 3: A CASE STUDY - INVASIVE MENINGOCOCCAL DISEASE (IMD)

In the previous chapter, vaccine perception and preferences were assessed in adolescents. The results showed that adolescents prefer vaccines targeting severe diseases with low costs. An example of a severe vaccine preventable disease is IMD. The highest peak in incidence of IMD occurs among 0 to 4 year olds, with a second peak of IMD during adolescence, attributed partially to the higher pharyngeal carriage rate of the bacteria during this stage of life compared to other age groups [18-20].

Taking IMD as an example, the burden of IMD was further investigated. Inclusion of MenB vaccines on the publicly funded immunisation schedules has been rejected in several countries such as Canada and Spain. If the vaccine is not provided free under the national immunisation program, the vaccine price is a financial barrier to achieving a high vaccine coverage rate [79]. A better understanding of the burden of IMD may assist in improving vaccine acceptance, addressing vaccine hesitancy, and informing future cost-effectiveness analyses and funding decisions regarding new meningococcal vaccine programs.

The chapter aims to answer the third research question and is outlined as follows: Sections 3.1.1 - 3.1.3 demonstrate the extent of the clinical and financial burden arising from IMD by evaluating the outcomes of IMD. Section 3.1.4 reviews the development of meningococcal vaccines.

3.1 LITERATURE REVIEW (incl. a systematic review and meta-analysis)

IMD is one of the most common causes of death from infectious diseases in childhood in developed countries [80]. IMD is caused by the bacterium *N. meningitidis*. *N. meningitidis* strains are traditionally classified into serogroups based on serological typing [81]. There are 13 known serogroups (A, B, C, D, E, H, I, K, L, W, X, Y and Z) causing IMD. These serogroups are distinguished by differences in surface polysaccharides of the outer membrane capsule. Globally, serogroups A, B, C, W and Y are the most common causes of the disease [82,83]. Four major serogroups (B, C, W and Y) cause most IMD cases in Australia [84]. The Meningococci can be further differentiated by differences in their outer membrane proteins and are referred to as serotypes, serosubtypes and immunotypes. Due to insufficient discrimination and limitations associated with serological typing methods [85], molecular typing (e.g. multilocus enzyme electrophoresis (MLEE), multilocus sequence typing (MLST), etc.) has been developed and used to characterise meningococcal strains [23] and complement serological classification. MLST has become a preferred method to classify meningococcal strains into different sequence types (STs) [86]. Meningococci with clonal complexes such as ST-5, ST-11, ST-32 or ST-41/44 show an increased tendency to cause invasive infections or disease outbreaks [23,81,87].

Approximately 150 - 300 cases of IMD are notified each year in Australia, with the highest notification rates occurring in Northern Territory followed by Tasmania, South Australia, Western Australia, Victoria, Queensland and New South Wales in 2017 [88]. MenB disease predominated nationally before 2015 [89]. MenW became the dominant serogroup in 2016 and 2017 due to a rise in incidence of MenW disease [84,88,90]. However, MenB is still the predominant serogroup in South Australia [35] and nationally in the first two quarters of 2018 [89].

Whilst IMD in Australia affects all age groups, the surveillance data show a bimodal age distribution with the highest rate in the 0 to 4 year age group and a second peak in the 15 to 25 year age group [88]. The age specific annual average hospitalisation rate (19.7/100,000) and death rate (0.85/100,000) were highest in infants aged less than one year [91].

Limited research has been conducted to evaluate the clinical and financial burden of the disease, especially in Australia [92-97]. IMD has been a notifiable disease since 1991. Surveillance of this disease within Australia is carried out by the National Notifiable Disease Surveillance System (NNDSS) with additional laboratory surveillance completed by the National Neisseria Network (NNN). However, The NNDSS and NNN concentrate on meningococcal strain characterisation and only collect basic demographic details such as age. More detailed clinical information and outcomes are not captured sufficiently to estimate the burden of IMD.

To answer the third research question an extensive systematic review was conducted to evaluate the clinical and financial burden of the disease using electronic databases: PubMed, Embase, and the Cochrane Library. The following keywords were used to develop search strategies: meningococcal, meningococcal meningitis, meningococcal septicaemia, *Neisseria meningitidis* AND burden, costs, cost analysis, fees, hospital charges, economic model, economics, expenditure, utilisation, case fatality, complications, sequelae, morbidity, mortality, death rates, incidence, survival analysis, health status. The final search terms included combinations of Medical Subject Headings (MeSH)/Emtree and text words contained in the title and abstract (See Appendix: IMD systematic review protocol). Meta-analyses were performed to estimate CFRs by age and serogroup, and the results are included in Section 3.1.1. The most common sequelae

identified in the systematic review are summarised in Section 3.1.2. The systematic review results regarding financial costs associated with IMD are presented in Section 3.1.3.

To further understand available vaccine programs against the disease, a literature review was performed. The literature review pertinent to vaccine development and vaccine strategies is presented in Section 3.1.4.

3.1.1 MORTALITY CAUSED BY MENINGOCOCCAL DISEASE

Despite timely access to healthcare services, IMD can still cause severe outcomes such as death. After systematically reviewing the literature, all published evidence pertinent to IMD associated mortality was quantitatively synthesised. The effects of age and serogroup on CFRs were further explored by using appropriate statistical methods. A manuscript titled “Case fatality rates of invasive meningococcal disease by serogroup and age: A systematic review and meta-analysis” has been prepared and submitted to the journal “Vaccine” for publication (accepted).

3.1.1.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Case fatality rates of invasive meningococcal disease by serogroup and age: a systematic review and meta-analysis
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Wang B, Santoreneos R, Giles L, Haji Ali Afzali H, Marshall H. Case fatality rates of invasive meningococcal disease by serogroup and age: a global systematic review and meta-analysis. Lancet Infectious Disease (submitted)

Principal Author

Name of Principal Author (Candidate)	Bing Wang		
Contribution to the Paper	BW conceived and designed the study, conducted database searches, extracted, analysed and interpreted data, performed quality assessment, and produced the first draft of the manuscript.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Renee Santoreneos		
Contribution to the Paper	RS extracted data, performed quality assessment, and reviewed the manuscript.		
Signature		Date	18/10/18

Name of Co-Author	Lynne Giles		
Contribution to the Paper	LG conceived and designed the study, resolved divergencies, instructed and assisted BW in data analysis, and contributed to, reviewed and edited the manuscript.		
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Name of Co-Author	Hossein Haji Ali Afzali		
Contribution to the Paper	HHAA conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/2018

Name of Co-Author	Helen Marshall		
Contribution to the Paper	HM conceived and designed the study, resolved divergencies, and contributed to, reviewed and edited the manuscript.		
Signature		Date	04 OCT 2018

Please cut and paste additional co-author panels here as required.

3.1.1.2 PUBLICATION

Title: Case fatality rates of invasive meningococcal disease by serogroup and age: A systematic review and meta-analysis

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ABSTRACT

INTRODUCTION

Invasive meningococcal disease (IMD) is uncommon but still causes considerable public health burden due to its high mortality and morbidity. This review aims to quantitatively synthesise all published evidence pertinent to mortality caused by IMD and assess the effect of age and serogroup on case fatality rates (CFRs).

METHODS

The PubMed and Embase databases, and the Cochrane Library were searched. Articles reporting national CFRs and published in English between January 2000 and May 2018 were eligible. The studies reporting mortality resulting from a specific symptom of IMD (e.g. meningococcal meningitis) were excluded. Mixed-effects logistic regression with a restricted cubic spline was used to analyse CFRs as a function of age. Random-effects meta-analyses were performed to estimate an overall CFR and CFRs by serogroup.

RESULTS

Among 48 eligible studies reporting national CFRs, 40 studies were included in meta-analyses representing 163,758 IMD patients. CFRs ranged from 4.1% to 20.0% with the pooled overall CFR of 8.3% (95% confidence interval (CI): 7.5%-9.1%). Serogroup B was associated with a lower pooled CFR (6.9% (95%CI: 6.0%-7.8%)) than other serogroups (W: 12.8% (95%CI: 10.7%-15.0%); C: 12.0% (95%CI: 10.5%-13.5%); Y: 10.8% (95%CI: 8.2%-13.4%)). The meta-analysis was not performed for serogroup A (MenA) cases due to a small number of MenA patients who were enrolled in eligible studies. For laboratory confirmed IMD cases, the predicted CFR was 9.0% in infants, gradually decreased to 7.0% in 7-year olds, subsequently increased to 15.0% in young adults aged 28 years, stabilised between 15-20% in mid-aged adults and reached a high in elderly people.

CONCLUSIONS

Our findings can provide useful information for better understanding the mortality risks, and quantifying the burden associated with IMD mortality.

KEYWORDS

meningococcal; systematic review; case fatality rates; age; serogroup

ABBREVIATIONS

AIC	Akaike's information criterion
CFR	Case fatality rate
CI	Confidence interval
ICD	International Classification of Diseases
IMD	Invasive meningococcal disease
MenA	Meningococcal serogroup A disease
MenB	Meningococcal serogroup B disease
MenC	Meningococcal serogroup C disease
MenW	Meningococcal serogroup W disease
MenY	Meningococcal serogroup Y disease
MRR	Mortality rate ratio
OR	Odd ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses

HIGHLIGHTS

- Our review quantitatively estimated the risk of death following IMD.

- Our meta-analyses confirmed and quantified the effect of serogroup and age on CFRs.
- Adolescents and young adults had the higher risk of mortality than infants.
- Serogroup W disease resulted in a high CFR.

INTRODUCTION

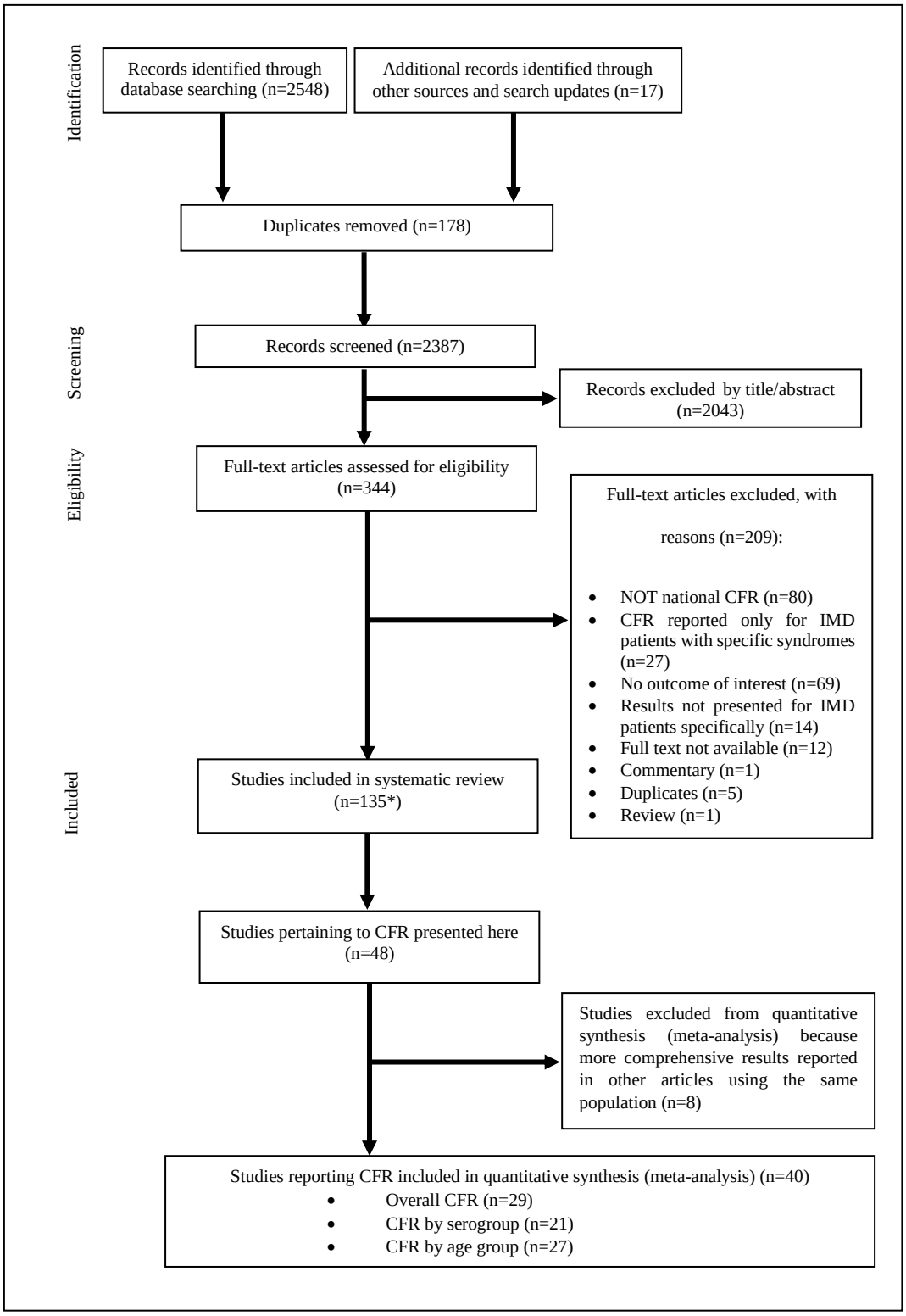
Neisseria meningitidis is estimated to be carried by around 10% of a healthy population and can result in invasive meningococcal disease (IMD), a life-threatening infection [1]. Vaccines have been developed to protect against serogroups A, B, C, W and Y, which are the most common serogroups causing IMD. The meningococcal serogroup C vaccine has been included on the national immunisation schedule for decades in many developed countries. New surface protein-based meningococcal serogroup B (MenB) vaccines have been recently developed and licensed in most developed countries. Quadrivalent (serogroups A, C, W, Y) conjugate vaccines have been included on the publicly funded immunisation schedule or are being considered for public funding in some countries. The evaluation of the cost-effectiveness of a vaccination program is one of the key inputs into the decision-making process. The cost-effectiveness of these preventive strategies depends on a number of factors including disease incidence, mortality, costs associated with the management of the disease and its sequelae, serogroup distribution, herd immunity, vaccine efficacy, and immunity duration. The case fatality rate (CFR) is not only an important parameter in cost-effectiveness evaluation, but also a key component in epidemiological studies and an essential measure of the burden of IMD. The mortality associated with IMD has been well documented in disease surveillance reports especially in developed countries [2-6], and frequently discussed in review articles [7-11]. Key factors such as age and serogroup have been reported as important factors influencing IMD outcomes [2,7,9]. However, the CFR has not been quantified and key factors such as age and serogroup in estimating CFRs have yet to be explored in a meta-analysis. In this paper, we conducted a systematic review and meta-analysis to identify published contemporary evidence worldwide, to estimate the CFR, and to investigate the impact of age and serogroup on CFRs.

METHODS

Search strategy and selection criteria

A search of the literature was conducted using electronic databases: PubMed, Embase, and the Cochrane Library. Primary search strategies identified articles that reported the clinical and financial burden of IMD using the following keywords: meningococcal, meningococcal meningitis, meningococcal septicaemia, Neisseria meningitidis AND burden, costs, cost analysis, fees, hospital charges, economic model, economics, expenditure, utilisation, case fatality, complications, sequelae, morbidity, mortality, death rates, incidence, survival analysis, health status. The final search terms included combinations of Medical Subject Headings (MeSH)/Emtree and text words contained in the title and abstract (Supplementary Table 1). Only studies pertaining to CFRs are presented here (Figure 1). The systematic review regarding the financial burden associated with IMD was published elsewhere [12]. Grey literature available online was searched for relevant abstracts and/or posters from the following organisations: Meningitis Research Foundation, Infectious Diseases Society of America, International Pathogenic Neisseria Conference, European Society for Paediatric Infectious Diseases, International Congress on Infectious Diseases, World Society for Pediatric Infectious Diseases, and Australian Society for Infectious Diseases. Emails were sent to the first authors for additional information as required. Reference lists of relevant review articles [7,9,11] were searched for additional citations of interest. The search was conducted by one reviewer (BW) on 3 August 2016 and updated on 3 May 2018.

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for article inclusion and exclusion



* The full systematic review aimed to estimate clinical and financial burden of IMD. Only studies reporting CFRs are presented here.

The article selection process occurred in two phases: 1) title and abstract screen: titles and abstracts of articles identified from the electronic databases and from Internet searches were reviewed; 2) full text review: the full text of articles selected at the title and abstract screen were obtained and reviewed for eligibility. The screening process was completed according to a predefined protocol.

Studies were eligible if national IMD CFRs were reported through primary data collection. Studies only reporting mortality resulting from a specific symptom of IMD (e.g. meningococcal meningitis) were excluded. Comments, letters, editorials, case reports, and reviews were excluded. Following the first publicly funded meningococcal C (MenC) vaccine program in the UK in 2000, several countries have added MenC vaccine onto their national immunisation programs. Since the epidemiology of IMD might be affected by the large scale implementation of MenC vaccine programs, the search was restricted to articles published from 1 January 2000 to 3 May 2018.Studies reported in languages other than English were excluded. Several national population or surveillance-based studies replicated data by containing patient populations which were completely included in other studies; in these instances, the publication with more comprehensive information presented was selected in meta-analyses to avoid double counting of evidence.

Reporting and performing this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 statement [13] and meta-analysis of observational studies in epidemiology guidelines [14]. All analyses were performed using Stata 14.2. This systematic review was registered with PROSPERO (CRD42016043213).

Data extraction and analysis

Data were independently extracted by two reviewers (BW and RS). The following characteristics of each study were collected: type of study including study design, setting and study period, study population (sample size, mean or median age at illness, serogroup, case definition, etc.), country, follow-up duration, outcomes (sequelae, CFR and costs relevant to IMD), and funding.

The Joanna Briggs Institute Critical Appraisal Tools were used to assess studies reporting the clinical burden of IMD including case-control, case series, cohort, quasi-experimental (non-randomised experimental studies), and randomised controlled studies [15]. Two independent reviewers (BW and RS) assessed the quality of studies, and any divergence between them was resolved through discussion. When disagreement was not resolved, senior researchers (HM and LG) were consulted. Through quality assessment, we found demographics and follow-up period of the study patients were not reported in a large number of studies. However, most studies reported national surveillance results and surveillance networks might receive limited demographic and follow-up information.

Meta-analyses were performed for overall CFR and CFRs by serogroup. Heterogeneity was assessed statistically using the I^2 statistic. Because substantial variability (heterogeneity) was expected across studies, a DerSimonian-Laird random-effects model was used [16].

Since we expected the relationship between CFRs and age to be non-linear, multilevel mixed-effects logistic regression (QR decomposition) with a restricted cubic spline was used to model CFRs as a function of age. As patient individual level data were not available, aggregate data for each age group in a study were used. The outcome measure

was the number of deaths observed in the study population recorded in binomial form, with denominator the number of IMD cases in the study population. We estimated the mean age for each age group using midpoint age of an age band if the true mean age was not presented. The model also included covariates: case definition, enrolment period, study and country. Different case definitions were used in various population studies and national surveillance networks, and therefore studies were classified into two groups: definite laboratory confirmed cases of IMD and notified cases of IMD. The notified cases of IMD included a combination of laboratory confirmed, probable and clinically diagnosed IMD. Studies were assigned to a decade in which most of study patients were enrolled if the study spanned more than one decade. For open-ended older age bands, an upper age limit of 99 years was chosen to calculate a midpoint of this age group, as the highest age limit of 99 years was used in the included study [17]. Studies were excluded from the regression analysis if the study population was only divided into two groups, adults and children, without specific age ranges.

The model was adjusted by case definition and enrolment period as fixed effects, with study nested within country as nested random effects. Fixed effects were used for those variables based on the assumption of a constant effect across all studies. The enrolment period (decade of study) was removed from the final regression model due to a lack of statistical significance. The variables selected for random effects were assumed to have random intercepts normally distributed with common variance and population mean. The model allows for multi-levels of nested clusters of random effects, on the assumption that observations within the same cluster are correlated. This model structure was decided a priori based on previous research [1,18] and the assumption that CFR by age has the same shaped curvilinear relationship across countries but estimates in a specific country might be higher or lower than the mean value. The adequacy of models containing a

restricted cubic spline with different numbers and locations of knots were assessed using Akaike's information criterion (AIC). The restricted cubic spline with five knots placed at the ages of 0.5, 7, 17, 42 and 82 years based on Harrell's recommended percentiles [19] was chosen because of the lowest AIC.

In sensitivity analyses, studies in French South Pacific Islands (New Caledonia) [20], Israel [21] and Kuwait [22] were excluded. Studies in European countries, Australia, the US and Canada were retained because these latter countries have comparable national surveillance systems. Saudi Arabia [23] was also excluded in the sensitivity analyses because the epidemiology of meningococcal disease was affected by Hajj and Umrah in Saudi Arabia.

RESULTS

Forty-eight studies met inclusion criteria and reported national CFRs in 34 countries (Table 1). Seven studies [24-30] were not included in meta-analyses due to data overlapping with other published reports that were included in the meta-analyses. IMD cases in these seven studies were completely included in other studies. Another study was excluded from meta-analysis because all-cause mortality rates within the first year of diagnosis of IMD were reported [31]. One article was available as a conference abstract and additional information was provided by the first author [32]. In total, 11807 deaths were observed in 163758 IMD patients. Although the review was limited to articles published after 2000, the observation time reported in studies spanned the period from 1974 to 2017 with most data reported from developed countries (e.g. the EU, the US, Canada, and Australia). Around half of studies (n=19, 47.5%) enrolled laboratory confirmed IMD patients only. Among 40 studies [2,4-6,17,20-23,32-62] included in the meta-analyses, 29 studies [4-6,17,20-23,32,34,35,38,42,43,45,46,48,49,51-58,60-62] were used to estimate the overall CFR with 21 studies [4-6,17,20,23,32,33,39,44,46,48,49,52-56,58,61,62] used to derive pooled estimates of CFRs by serogroup, and 28 studies [2,4,17,20,21,23,33,35-37,39-43,47,48,50-55,58-62] used to examine the age effect on CFR.

Table 1: Characteristic of eligible studies identified through systematic review

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
1.	Archer et al (2017) [33]	Australia	1999-2015	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B & C	All	4774 (B&C)	By age and serogroup: <5 years: B: 5%, C: 5%; 5-9 years: B: 2%, C: 8%; 10-14 years: B: 1%, C: 2%; 15-24 years: B: 2%, C: 6%; 25+ years: B: 6%, C: 12%; all ages: B: 4%, C: 8%
2.	Baker et al (2001) [34]	New Zealand	1991-2000	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	3547	Overall: 4.5%; laboratory confirmed cases: 4.9%
3.	Ben-Shimol et al (2013) [21]	Israel	1989-2010	Hospital based national surveillance	Laboratory (culture) confirmed cases	All	<15 years	743	Overall: 9.9%; by age: <1 year: 9.2%, 1–4 years: 12.3%, >4 years: 7.7%; yearly mean CFR: 9.9% ± 4.1%
4.	Brotherton et al (2004) [35]	Australia	2001-2002	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	1355	88 deaths in 1355 cases; by age: 0-4 years: 26/393, 5-14 years: 8/213, 15-24 years: 21/391, 25-59 years: 24/286, 60+ years: 9/72

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
5.	Brotherton et al (2007) [36]	Australia	2003-2005	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	1355 (2003-2005); 955 (2003-2004)	69 deaths in 1355 cases in 2003-2005; 46 deaths in 955 cases in 2003-2004 (using IMD notification numbers reported from national notifiable diseases surveillance system): 0-4 years: 12/292, 5-14 years: 1/116, 15-24 years: 12/273, 25-59 years: 10/199, 60+ years: 11/74
6.	Chiu et al (2010) [37]	Australia	2005-2007	National surveillance based on notification and hospital data	Laboratory confirmed and probable cases	All	All	622 (2006-2007); 700 (2005-2006)	32 deaths in 700 cases in 2005-2006 (using IMD notification numbers reported from national notifiable diseases surveillance system): 0-4 years: 15/242, 5-14 years: 2/84, 15-24 years: 3/177, 25-59 years: 7/153, 60+ years: 5/44; 21 deaths in 622 cases in 2006-2007
7.	Cizman et al (2001) [38]	Slovenia	1993-1999	Hospital based national surveillance	Laboratory confirmed cases	All	<15yrs (1993-1999); all (1995-1999)	75	4.1%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
8.	Darton et al (2009) [39]	England and Wales, UK	1999-2001	National surveillance based on laboratory data	Laboratory confirmed cases	All	All	1910 (EDTA-treated blood samples were received by the Meningococcal Reference Unit)	Overall: 10%; by age: <1 year: 45/482, 1-3 years: 15/397, 4-11 years: 12/272, 12-17 years: 33/315, 18-20 years: 7/90, 21-60 years: 40/274, 61+ years: 18/59; by serogroup: A: 0/1, B: 62/1010, C: 94/616, Y: 0/8, W: 2/31, ungrouped: 10/202
9.	Daures et al (2015) [20]	French South Pacific Islands (New Caledonia)	2005 - 2011	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	66 episodes including 2 recurrences (n=64)	Overall: 7.8%; by age: <1 year: 2/4, 1-4 years: 2/12, 5-9 years: 0/10, 10-14 years: 0/11, 15-19 years: 0/10, 20-24 years: 0/9, 25-34 years: 0/1, 35-44 years: 1/2; 45-54 years: 0/1, 55-64 years: 0/3, 65-74 years: 0/2, 75+ years: 0/1; by serogroup: B: 3/29

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
10.	Davison et al (2002) [40]	England and Wales, UK	July 1993-June 1998	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	C	All	Actual laboratory confirmed MenC cases: 2782; estimated confirmed MenC cases: 3360	CFRs in estimated laboratory confirmed cases by age: <1 year: 5.3%, 1-4 years: 7.3%, 5-9 years: 4.7%, 10-14 years: 7.9%, 15-19 years: 13.9%, 20-24 years: 12.9%, 25-29 years: 14.6%, 30-34 years: 13.3%, 35-39 years: 17.9%, 40+ years: 18.3%
11.	de Greeff et al (2008) [24]	Netherlands	January 2003-May 2005	National surveillance based on notification data	Laboratory confirmed cases	All	All	752	Overall: 6.7%; by serogroup: B: 6.3%, C: 5.2%
12.	Dey et al (2016) [41]	Australia	2008-2011	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	1015	Overall: 48/1015; by age: <1 year: 10/163, 1-4 years: 5/184, 5-14 years: 1/118, 15-24 years: 9/266, 25-49 years 10/154, 50-64 years: 5/77, 65+ years: 8/53

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
13.	Edge et al (2016) [2]	England, UK	2007-2011	National population linkage study	Laboratory confirmed cases	All	All	4619	30-day CFR: 4.5%; overall CFR (after 30 days): 4.7%; by age: <1 year: 3.3%, 1-4 years: 3.0%, 5-14 years: 2.2%, 15-24 years: 5.4%, 25-44 years: 3.7%, 45-64 years: 4.7%, 65+ years: 18.0%; by serogroup: B: 4.2%, C: 3.4%, W: 9.5%, Y: 9.9%, other: 0.7%
14.	Gil-Prieto et al (2011) [42]	Spain	1997-2008	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on International Classification of Diseases (ICD) codes	All	All	11611	Overall: 7.3%; by age: <1 year: 5.2%, <2 years: 5.1%, 0-4 years: 5.0%, 5-9 years: 3.6%, 10-14 years: 4.6%, 15-19 years: 8.7%, 20-24 years: 9.5%, 25-29 years: 10.2%, 30-49 years: 9.8%, 50-54 years: 12.6%, 55-59 years: 12.4%, 60-64 years: 15.1%, 65-69 years: 15.2%, 70-74 years: 14.7%, 75-79 years: 20.2%, 80-84 years: 29.5%, 85+ years: 37.7%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
15.	Goldacre et al (2013) [43]	England, UK	1999-2010	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on ICD codes	All	All	19113	30-day CFR: 4.9%; by age: <1 year: 3.0%, 1-4 years: 2.9%, 5-9 years: 1.6%, 10-14 years: 3.8%, 15-19 years: 5%, 20-24 years: 4.1%, 25-29 years: 5.5%, 30-34 years: 7.2%, 35-39 years: 8.7%, 40-44 years: 8.0%, 45-49 years: 9.5%, 50-54 yeas: 7.5%, 55-59 years: 14.3%, 60-64 years: 12.9%, 65-69 years: 20.8%, 70-74 years: 16.5%, 75-79 years: 19.0%, 80+ years: 32.5%
16.	Gottfredsson et al (2006) [44]	Iceland	1977-2004	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	362	Overall: 8.6%; by serogroup: B: 14/204, C: 14/144, others: 3/14
17.	Gottfredsson et al (2011) [45]	Iceland	1975-2004	Population based study	Laboratory confirmed cases	All	All	541	30-day CFR: 7.9%
18.	Gray et al (2006) [46]	England and Wales, UK	July 1993-June 2004	National surveillance based on laboratory data	Laboratory confirmed cases	All	All	21712	Overall: 6.7%; by serogroup: B: 5.1%, C: 11.6%, others: 5.0%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
19.	Hanquet et al (2014) [47]	Belgium	2004-2010	National surveillance based on hospital discharge and laboratory data	Laboratory confirmed cases	All	All	933	Overall: 7.0%; by serogroup: B: 5.4%, C: 15.6%; by age: <1 year: 6.7%, 1-4 years: 4.9%, 5-9 years: 3.2%, 10-19 years: 4.2%, 20-64 years: 10.3%, 65+ years: 16.3%
20.	Howitz et al (2009) [48]	Denmark	1974-2007	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	5924	31-day CFR: 7.6%; by age: <1 year: 5.9%, 1–4 years: 7.5%, 5–9 years: 3.5%, 10–19 years: 5.6%, 20–49 years: 9.4%, 50+ years: 17.9%; by serogroup: A: 3.9%, B: 7.9%, C: 9.1%, W: 10.3%, other known: 17.0%
21.	Husain et al (2015) [22]	Kuwait	1987-2013	National surveillance study	Laboratory confirmed cases	All	All	293	13.5%
22.	Knol et al (2017) [25]	Netherlands	July 2015-March 2017	National surveillance based on notification and laboratory data	Laboratory confirmed cases	W	All	79	11%
23.	Knol et al (2018) [49]	Netherlands	2015-2017	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B, W	All	215 (B); 138 (W)	W: 12%, B: 4%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
24.	Ladhani et al (2012) [26]	England and Wales, UK	July 2006-June 2011	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	5471	Overall: 5.3%; by serogroup: B: 5.2%, C: 9.9%, Y: 9.2%, W: 5.5%
25.	Ladhani et al (2012) [27]	England and Wales, UK	2007-2009	National surveillance based on notification and laboratory data	Laboratory confirmed cases	Y	All	143	19% for all MenY cases in 2009; 13% for 114 genotypically characterized isolates in 2007-2009
26.	Ladhani et al (2015) [50]	England and Wales, UK	July 2008-June 2014	National surveillance based on notification and laboratory data	Laboratory confirmed cases	W	All	270	Number of death: 30/270; by age: <5 years: 2/65; 5-19 years: 5/43, 20-44 years: 5/35, 45-64 years: 4/49, 65+ years: 14/78
27.	MacNeil et al (2017) [4]	US	2006-2015	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	7924	Overall: 14.9%; by age: <1 year: 8.6%, 1 year: 5.9%, 2-4 years: 11.8%, 5-10 years: 10.5%, 11-15 years: 11.5%, 16-20 years: 14.3%, 21-25 years: 16.7%, 26-44 years: 16.8%, 45-64 years: 16.9%, 65-84 years: 17.4%, 85+ years: 28.0%; by serogroup: B: 11.5%, C: 20.2%, W: 20.9%, Y: 13.7%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
28.	Martin et al (2016) [5]	Australia	2003-2015	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	3720 (all IMD); 159 (W)	Overall: 4.7%; by serogroup: B: 4.2%, C: 9.1%, W: 10.7%, Y: 4.1%
29.	McDonald et al (2014) [32]	Scotland, UK	1999-2013	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B	All	1028	B: 5.7%
30.	McIntyre et al (2002) [51]	Australia	1998-2000	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	1655 (1998-2000)	103 deaths in 1655 cases (1998-2000) (using IMD notification numbers reported from national notifiable diseases surveillance system in 1998): 0-4 years: 33/588, 5-14 years: 8/208, 15-24 years: 25/492, 25-59 years: 28/289, 60+ years: 9/78
31.	Memish et al (2013) [23]	Saudi Arabia	1995-2011	National surveillance based on notification data	Laboratory confirmed cases	All	All	1103	Overall: 18.0%; by age: <1 year: 6.8%, 1-4 years: 9.4%, 5-14 years: 9.3%, 15-45 years: 19.4%, 46+ years: 32.6%; by serogroup: A: 21.8%, B: 21.2%, C: 20%, W: 19.7%, Y: 33.3%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
32.	Montero et al (2009) [28]	Spain	1997-2005	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on ICD codes	All	All	9479	Overall: 6.5%; by age: 0-4 years: 4.7%, 5-9 years: 3.4%, 10-14 years: 3.8%, 15-19 years: 7.9%, 20-24 years: 8.7%, 25-29 years: 11.8%, 30+ years: 12.2%
33.	Muscat et al (2009) [52]	Malta	1994–2007	National surveillance based on notification data	Laboratory confirmed, probable and possible cases	All	All	233	Overall: 12%; by age: < 1 year: 7%, 1-9 years: 6%, 10-19 years: 13%, 20-44 years: 13%, 45+ years: 23%; by serogroup: B: 13/87, C: 5/18
34.	Parent du Chatelet et al (2017) [53]	France	2006-2015	National surveillance based on notification data	Laboratory and clinically diagnosed cases	All	All	5894	Overall: 10.4%, by age: <1 year: 9.9%, 1-4 years: 8.9%, 5-14 years: 5.9%, 15-24 years: 10.3%, 25-59 years: 9.3%, 60+ years: 20.0%; by serogroup: B: 8.8%, C: 13.2%, W: 11.9%, Y: 15.5%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
35.	Parikh et al (2018) [54]	England, UK	January 2011-June 2015	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	3411	28-day CFR: 6.9%; by age: <1 year: 4.0%, 1-4 years: 4.8%, 5-14 years: 4.8%, 15-24 years: 6.2%, 25-44 years: 7.8%, 45-64 years: 6.3%, 65-74 years: 12.7%, 75-84 years: 17.0%, 85+ years: 31.9%; by serogroup: B: 5.4%, C: 10.1%, W: 11.9%, Y: 12.1%
36.	Perrocheau et al (2005) [17]	France	2001-2003	National surveillance based on notification data	Laboratory and clinically diagnosed cases	All	All	1707 (2001-2003)	Overall: 14.0%; by age: < 2 years: 15.3%, 2-14 years: 11.2%, 15-24 years: 9.6%, 25-99 years: 21.1%; by serogroup: B: 11.3%, C: 17.9%, W: 20.0%
37.	Piscopo et al (2000) [29]	Malta	1994-1998	National surveillance based on hospital data	Lab confirmed and probable cases	All	All	60	20.0%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
38.	Roed et al (2010) [31]	Denmark	1977-2006	National surveillance based on hospital register data	All hospital discharges of meningococcal infections based on ICD codes	All	All	5356	All-cause mortality: within the first year of diagnosis of IMD: 8.3%; during the observation period: 6.4%: overall mortality rate ratio (MRR): 1.27 (95%CI: 1.12-1.45), adjusted MRR: 1.21 (95%CI: 1.06-1.37), adjusted MRR for death due to nervous, digestive and genitourinary system diseases, respectively: 3.15 (95%CI: 1.59-6.23), 1.99 (95%CI: 1.16-3.43), 6.26 (95%CI: 1.58-24.81)
39.	Ruedin et al (2004) [55]	Switzerland	1999-2002	National surveillance based on notification data	Laboratory confirmed and probable cases	All	All	626	Overall: 9.1%; by age: <1 year: 6.8%, 1-4 years: 15.1%, 5-9 years: 2.8%, 10-19 years: 4.0%, 20-29 years: 11.9%, 30+ years: 12.2%; by serogroup: B: 8.3%, C: 8.5%, other or unknown: 10.8%
40.	Sadarangani et al (2015) [56]	Canada	2002-2011	Population based surveillance study	Laboratory confirmed cases	All	All	868	Overall: 8.4%; by serogroup: A: 50.0%, B: 6.1%, C: 12.8%, W: 8.7%, Y: 9.5%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
41.	Schrauder et al (2007) [57]	Germany	2003	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	779 cases reported to the Robert Koch Institute; 565 laboratory confirmed cases isolated/typed at the National Reference Centre for Meningococci	8.8%
42.	Shigematsu et al (2002) [58]	England, Wales and Northern Ireland, UK	January1999 -June 2001	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	12074	Overall: 5.8%; laboratory confirmed cases: 8.2%; probable cases: 2.5%; laboratory confirmed CFR by age: <1 year: 6.1%, 1-4 years: 4.3%, 5-14 years: 4.8%, 15-17 years: 7.6%, 18+ years: 15.3%; by serogroup: B: 5.8%, C: 13.8%, W: 15.0%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
43.	Skoczynska et al (2013) [59]	Poland	2010-2011	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	458 (2010-2011)	During the period 2010-2011, overall: 10.0%; by age: 0-5 years: 10.3%, 5-9 years: 12.5%, 10-14 years: 5.6%, 15-19 years: 3.7%, 20-24 years: 15.4%, 25-44 years: 7.9%, 45-64 years: 2.9%, 65+ years: 46.2%; by serogroup: B: 10.3%, C: 8.8%
44.	Squires et al (2000) [61]	Canada	1997-1998	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	439	Overall: 8.9%; by serogroup: B: 5.4%, C: 12.4%, Y: 14.3%, others: 4.8%, clinical cases: 9.2%; number of death by age group for the year 1997 and 1998, respectively: <1 year: 1/47, 0/21; 1-4 years: 4/43, 0/39; 5-14 years: 1/39, 1/20; 15-19 years: 6/39, 1/24; 20-64 years: 9/73, 9/54; 65+ years: 6/24, 1/14

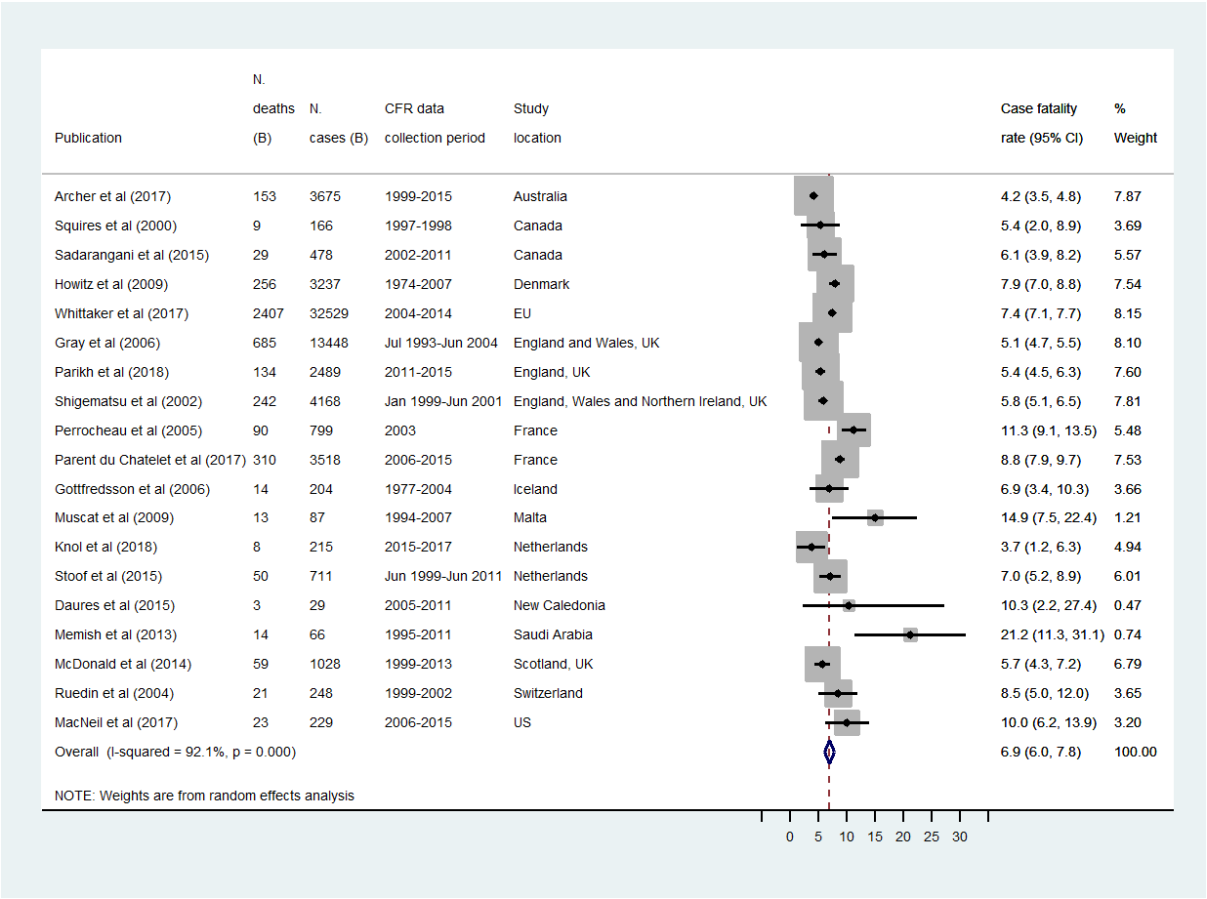
	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
45.	Squires et al (2004) [60]	Canada	1999-2001	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	805 (214 in 1999, 241 in 2000, 350 in 2001)	Overall: 10.7%, 8.7%, and 9.4% in 1999, 2000, and 2001 respectively; in 1999 by age: <1 year: 2.6%, 1-4 years: 8.30%, 5-9 years: 15.4%, 10-14 years: 20.0%, 15-19 years: 6.5%, 20-24 years: 12.5%, 25-64 years: 15.4%, 65+ years: 18.7%; in 2000 by age: <1 year: 10.5%; 1-4 years: 4.0%; 5-9 years: 11.8%; 10-14 years: 10.0%; 15-19 years: 6.0%; 20-24 years: 3.8%; 25-64 years: 12.3%, 65+ years: 11.1%; in 2001 by age: <1 year: 10.0%, 1-4 years: 9.1%, 5-9 years: 9.1%, 10-14 years: 6.2%, 15-19 years: 2.6%, 20-24 years: 6.5 %, 25-64 years: 15.2%, 65+ years: 15.2%
46.	Steindl et al (2011) [30]	Austria	2010	National surveillance based on notification and laboratory data	laboratory confirmed cases	All	All	80	12.5%

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
47.	Stoof et al (2015) [62]	Netherlands	June 1999-June 2011	National surveillance based on hospital and laboratory data	Laboratory confirmed cases	All	All	939	30-day CFRs: 8%; by age: 0-6 months: 2%, 6-24 months: 7%, 2-4 years: 5%, 5-9 years: 4%, 10-19 years: 4%, 20-64 years: 8%, 65+ years: 39%; by serogroup: B: 8%, C: 9%, W: 13%, Y: 13%
48.	Whittaker et al (2017) [6]	EU	2004-2014	National surveillance based on notification data	Laboratory confirmed cases	All	All	41206	Overall: 8.6%; by serogroup: B: 7.4%, C: 14.3%, W: 10.3%; Y: 10.2%

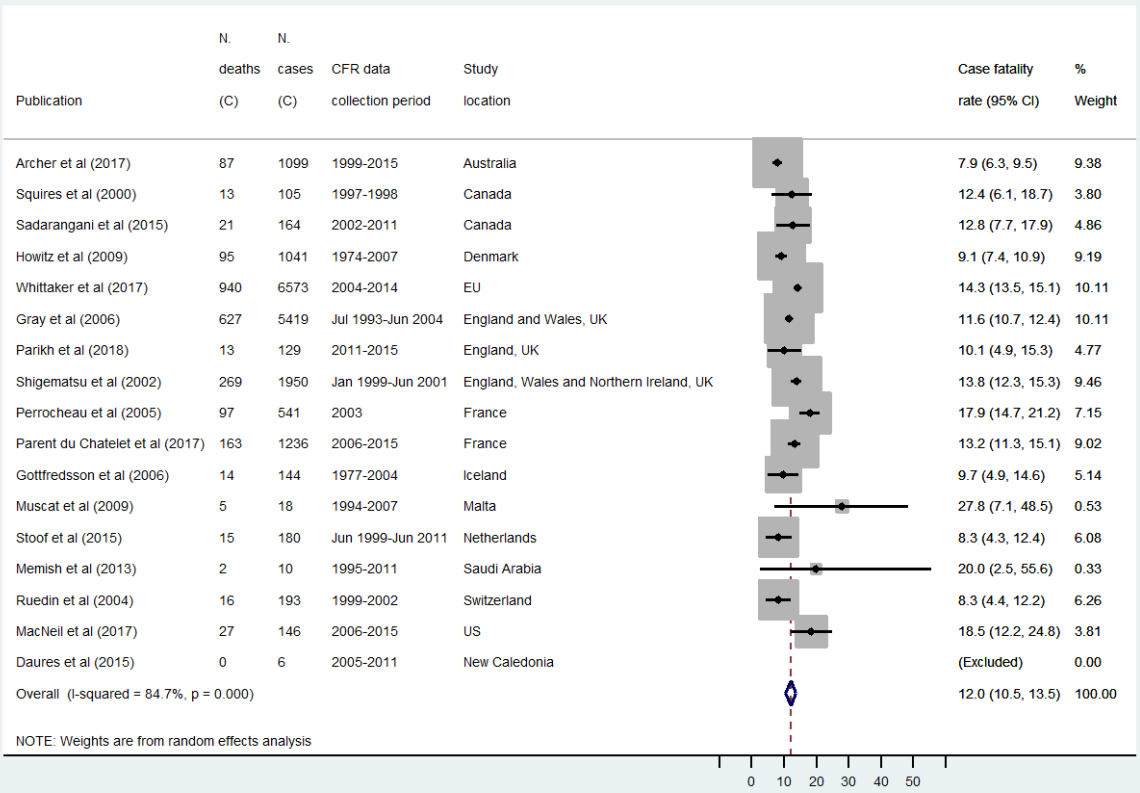
The overall CFR was estimated to be 8.3% and the included studies were very heterogeneous (I^2=96.3% (95% confidence interval (CI): 95.7%-96.8%)) (Supplementary Figure 1). Among 21 studies, 19 [4,6,17,20,23,32,33,44,46,48,49,52-56,58,61,62] reported CFRs in MenB cases (n= 67324) (Figure 2A); 17 [4,6,17,20,23,33,44,46,48,52-56,58,61,62] reported CFRs in MenC cases (n=18954) (Figure 2B); 13 [4-6,17,23,39,48,49,53,54,56,58,62] reported CFRs in serogroup W (MenW) cases (n= 3017) (Figure 2C); 10 [4-6,23,39,53,54,56,61,62] studies reported CFRs in serogroup Y (MenY) cases (n= 3356) (Figure 2D). The pooled estimate of MenB CFR was lower than serogroups W, C and Y. Heterogeneity reduced when meta-analyses were stratified by serogroup, especially in MenW and MenY cases. The number of serogroup A (MenA) cases was low in the identified studies. Only two of six studies enrolled more than ten MenA cases with CFRs ranging from 3.9% [48] to 21.8% [23]. Therefore, meta-analysis was not performed for MenA disease.

Figure 2: Forest plots for CFRs by serogroup

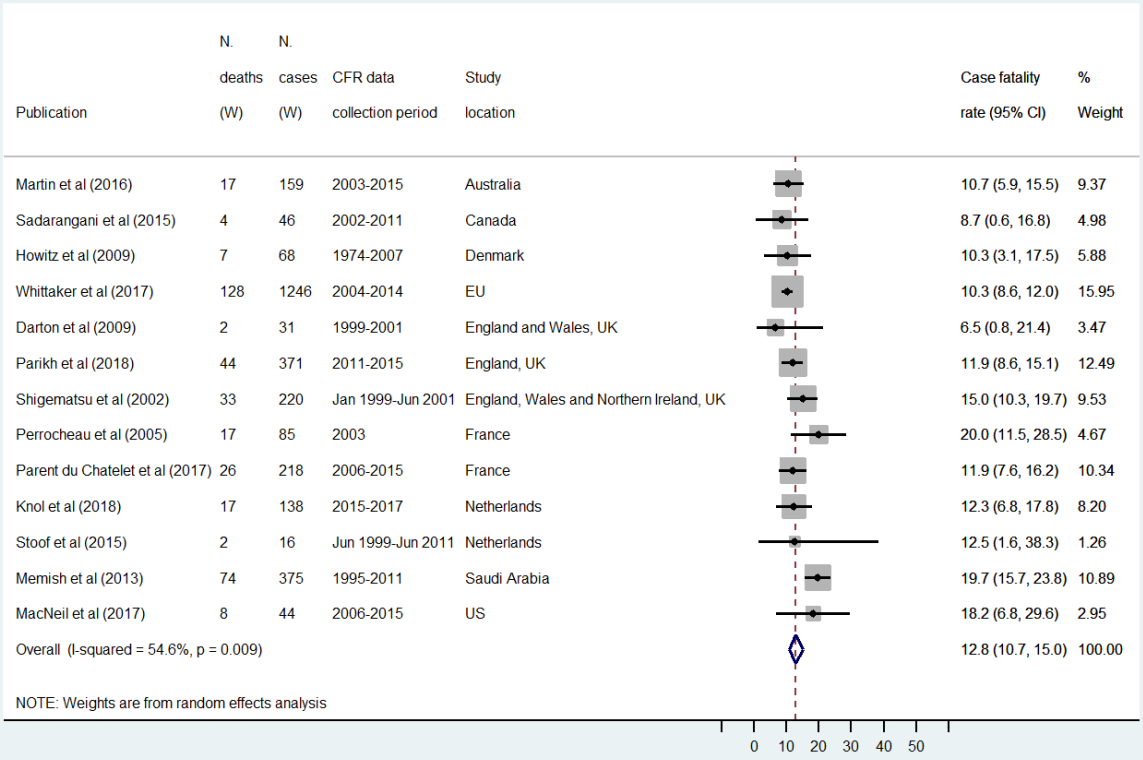
2A



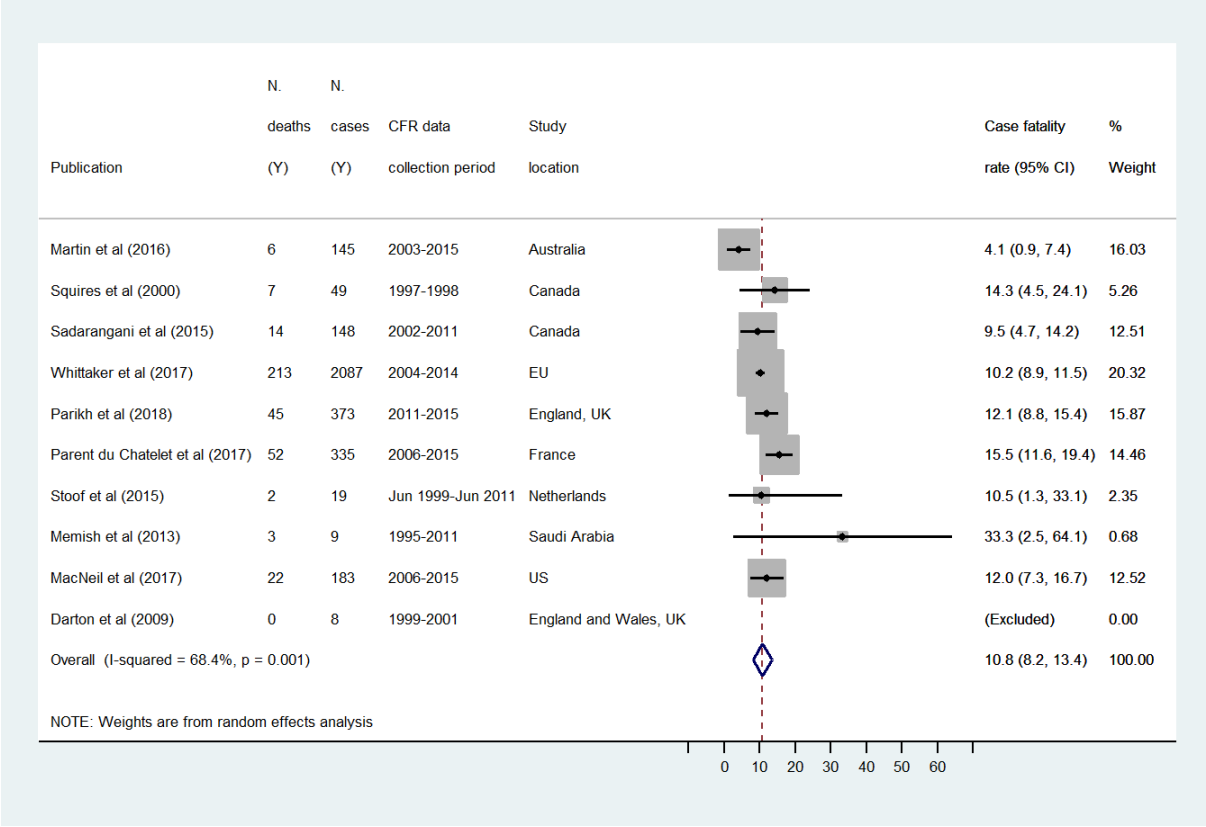
2B


Publication
N. deaths (C)
N. cases (C)
CFR data collection period
Study location
Case fatality rate (95% CI)
% Weight
Archer et al (2017) 87 1099 1999-2015 Australia 7.9 (6.3, 9.5) 9.38
Squires et al (2000) 13 105 1997-1998 Canada 12.4 (6.1, 18.7) 3.80
Sadarangani et al (2015) 21 164 2002-2011 Canada 12.8 (7.7, 17.9) 4.86
Howitz et al (2009) 95 1041 1974-2007 Denmark 9.1 (7.4, 10.9) 9.19
Whittaker et al (2017) 940 6573 2004-2014 EU 14.3 (13.5, 15.1) 10.11
Gray et al (2006) 627 5419 Jul 1993-Jun 2004 England and Wales, UK 11.6 (10.7, 12.4) 10.11
Parikh et al (2018) 13 129 2011-2015 England, UK 10.1 (4.9, 15.3) 4.77
Shigematsu et al (2002) 269 1950 Jan 1999-Jun 2001 England, Wales and Northern Ireland, UK 13.8 (12.3, 15.3) 9.46
Perrocheau et al (2005) 97 541 2003 France 17.9 (14.7, 21.2) 7.15
Parent du Chatelet et al (2017) 163 1236 2006-2015 France 13.2 (11.3, 15.1) 9.02
Gottfredsson et al (2006) 14 144 1977-2004 Iceland 9.7 (4.9, 14.6) 5.14
Muscat et al (2009) 5 18 1994-2007 Malta 27.8 (7.1, 48.5) 0.53
Stoof et al (2015) 15 180 Jun 1999-Jun 2011 Netherlands 8.3 (4.3, 12.4) 6.08
Memish et al (2013) 2 10 1995-2011 Saudi Arabia 20.0 (2.5, 55.6) 0.33
Ruedin et al (2004) 16 193 1999-2002 Switzerland 8.3 (4.4, 12.2) 6.26
MacNeil et al (2017) 27 146 2006-2015 US 18.5 (12.2, 24.8) 3.81
Daures et al (2015) 0 6 2005-2011 New Caledonia (Excluded) 0.00
Overall (I-squared = 84.7%, p = 0.000) 12.0 (10.5, 13.5) 100.00
NOTE: Weights are from random effects analysis
0 10 20 30 40 50

2C


Publication
N. deaths (W)
N. cases (W)
CFR data collection period
Study location
Case fatality rate (95% CI)
% Weight
Martin et al (2016) 17 159 2003-2015 Australia 10.7 (5.9, 15.5) 9.37
Sadarangani et al (2015) 4 46 2002-2011 Canada 8.7 (0.6, 16.8) 4.98
Howitz et al (2009) 7 68 1974-2007 Denmark 10.3 (3.1, 17.5) 5.88
Whittaker et al (2017) 128 1246 2004-2014 EU 10.3 (8.6, 12.0) 15.95
Darton et al (2009) 2 31 1999-2001 England and Wales, UK 6.5 (0.8, 21.4) 3.47
Parikh et al (2018) 44 371 2011-2015 England, UK 11.9 (8.6, 15.1) 12.49
Shigematsu et al (2002) 33 220 Jan 1999-Jun 2001 England, Wales and Northern Ireland, UK 15.0 (10.3, 19.7) 9.53
Perrocheau et al (2005) 17 85 2003 France 20.0 (11.5, 28.5) 4.67
Parent du Chatelet et al (2017) 26 218 2006-2015 France 11.9 (7.6, 16.2) 10.34
Knol et al (2018) 17 138 2015-2017 Netherlands 12.3 (6.8, 17.8) 8.20
Stoof et al (2015) 2 16 Jun 1999-Jun 2011 Netherlands 12.5 (1.6, 38.3) 1.26
Memish et al (2013) 74 375 1995-2011 Saudi Arabia 19.7 (15.7, 23.8) 10.89
MacNeil et al (2017) 8 44 2006-2015 US 18.2 (6.8, 29.6) 2.95
Overall (I-squared = 54.6%, p = 0.009) 12.8 (10.7, 15.0) 100.00
NOTE: Weights are from random effects analysis
0 10 20 30 40 50

2D



CFRs by age group were reported in 28 studies, including 83649 IMD cases. Among those cases, 22308 were definite laboratory confirmed cases with 61341 were defined as notified IMD cases (a combination of laboratory confirmed, probable and/or clinically diagnosed cases). Besides the variables created for the spline function of age, the type of case definition was significantly associated with CFR, after adjusting the nested random-effects of country and study (likelihood ratio test P<0.0001). At a given age, the chance of death for patients with laboratory confirmed IMD was double in comparison with those notified IMD cases (Table 2). The estimated variance in CFRs was higher for between studies than between countries. For laboratory confirmed cases, the predicted CFRs were highest in Saudi Arabia and lowest in Australia.

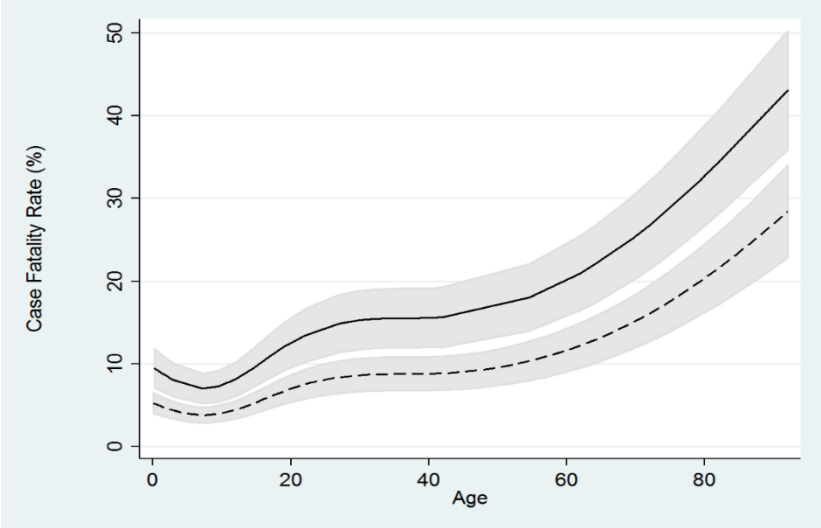
Table 2: Fixed and random effect estimates from the main analysis

Fixed effect parameter estimates:		
	Estimates	95%CI (p value)
Notified IMD cases (a combination of laboratory confirmed, probable or clinically diagnosed cases)	OR: 1	
Laboratory confirmed IMD cases	OR: 1.906	1.491-2.434 (p<0.0001)
Random effect parameter estimates		
Country	Variance: 0.080	0.020-0.331
Study	Variance: 0.127	0.057-0.284

Predicted CFRs by age were non-linear (Figure 3). Predicted CFRs for laboratory confirmed cases decreased from 9.0% in infants to 7.0% in 7-year olds, stayed stable in children aged 7-10 years, gradually increased to 10.4% in adolescents aged 16 years, reached a peak of 15.0% in young adults aged 28 years, remained steady in adults aged between 28 and 45 years, rose rapidly in older adulthood, and reached 32.8% in 80-year olds (Supplementary Table 2).

Figure 3: Estimates of CFR by age

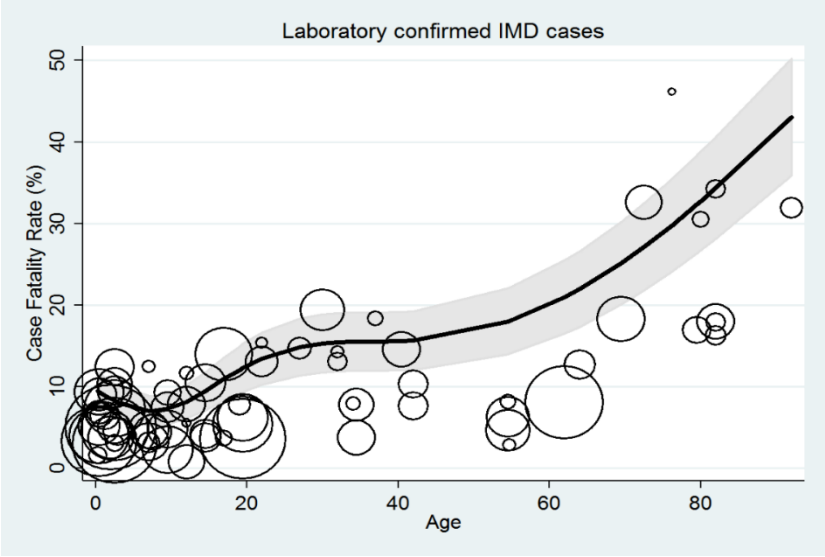
3A



—— Fitted values for laboratory confirmed IMD cases 95%CI

– – Fitted values for notified IMD cases

3B



○ Observed CFRs —— Fitted values 95%CI

The size of circles is proportional to the number of cases included in each study, with the larger circles indicating a larger sample size.

In the sensitivity analysis of studies reporting CFRs by age in the EU, the US, Canada and Australia only (n=25), laboratory confirmation of case was still a significant factor affecting CFRs (odd ratio (OR): 1.92; 95%CI: 1.48-2.49; p<0.0001). However, the predicted CFRs tended to be slightly lower in general compared with the main analysis, increasing to 10.1% in 16-year olds, remaining stable through young adulthood, and increasing to 32.2% in elderly patients aged 80 years. Similar to the main analysis, variation in CFRs was still lower between countries (0.092; 95%CI: 0.019-0.445) than between studies (0.137; 95%CI: 0.058-0.322).

After removing studies in New Caledonia, Israel, Kuwait and Saudi Arabia, the pooled estimates of overall, MenB and MenY CFRs were slightly lower: 7.8% (95%CI: 7.0%-8.6%; I^2=96.3% (95%CI: 95.6%-96.8%)), 6.8% (95%CI: 5.9%-7.6%; I^2=92.7% (95%CI: 90.3%-94.3%)), 10.6% (95%CI: 8.1%-13.2%; I^2=69.8% (95%CI: 19.2%-83.7%)), respectively. The pooled estimate of the MenW CFR dropped from 12.8% to 11.3% (95%CI: 10.1%-12.5%; I^2=0.0% (95%CI: 0.0%-49.8%)). The pooled estimate of MenC CFR stabilised at 12.0% (95%CI: 10.4%-13.5%; I^2=85.7% (95%CI: 77.8%-89.8%)).

DISCUSSION

This is the first meta-analysis to estimate the CFR and to quantitatively examine the effect of age and serogroup on CFRs.

The meta-analysis showed the greatest CFRs in MenW and MenC cases, which highlighted the significant impact of the recent increase in incidence of MenW disease in many countries. After removing fatality data reported in the Saudi Arabia, the pooled MenW CFR decreased and became lower than MenC in the sensitivity analysis. The reduction in the pooled estimate may reflect very high fatality associated with the MenW outbreak during Hajj in Saudi Arabia [63]. As we expected, a high level of heterogeneity was found in the synthesis of overall CFR. After analyses stratifying by serogroup, heterogeneity reduced especially in cases due to serogroup W and Y disease. This finding is reassuring as we expected serogroup was an important factor in predicting CFRs. However, heterogeneity was still high in MenB related cases. In our review, almost 70% of IMD cases were caused by MenB disease with diverse age groups and study design reflecting the epidemiology of MenB disease. Especially for endemic MenB disease, organisms causing the infection are genetically diverse, which may explain the heterogeneity in CFRs [64]. Previous research has demonstrated that certain serotypes/serosubtypes and clonal complexes were associated with a higher CFR [65-68]. For example, MenC disease of the phenotype 2a:P1.2,5 was associated with an increased risk of mortality [48]. MenW disease has traditionally been caused by strains of the ST-22 clonal complex which is usually associated with fatal disease outcomes in the elderly population. However, the recent rise in cases of MenW disease, which is caused by strains of the ST-11 clonal complex in many countries, can also be fatal in children and young adults [50].

Although the disease incidence peaks in infants and IMD remains a leading infectious cause of death in early childhood in developed countries [69], our regression model indicated that CFRs were lower in infants compared to adolescents and young adults. In addition to the highest carriage rate estimated in young adults aged 19 years [1], our finding of an increased CFR in young adults would help researchers and policy makers to further understand the potential impact of vaccination strategies. CFR doubled with age from 15% in young adults to 30% in those aged around 75 years. Reasons for the significant variation in CFR by age are not fully understood [9]. Higher prevalence of serogroup W and Y disease was observed in older people especially with underlying medical conditions [5,27,50,70,71]. The highest mortality rate may be explained by predominant serogroups and frailty. The highest CFR in elderly patients may also be associated with delay in appropriate treatment, because the symptoms may be more difficult to recognise in frail older patients coupled with a relatively lower prevalence of IMD in this age group. Moreover, factors related to host may explain different CFRs. For example, previous research reported genetic factors were clearly associated with mortality and severe outcomes of meningococcal disease [72-73].

Our regression model showed an increased variance between studies compared with between countries. After removing data collected in Israel, New Caledonia and Saudi Arabia in sensitivity analysis, the results still revealed the same trend. Although we did not limit our search to Western countries, most included studies were conducted in developed countries. The low variance between countries might be due to similar healthcare setting and comparable epidemiological transition across developed countries. Case definitions used by different studies varied substantially. For example, some studies [2,42] enrolled patients based on ICD codes at hospital discharge without laboratory confirmation; some studies used national surveillance or notification data. Even for

surveillance data, a number of studies [23,44,55] restricted IMD notification to laboratory confirmed cases, but several studies had included probable or clinically diagnosed cases [34-37,60,61]. Furthermore, laboratory confirmed cases were defined inconsistently in different studies [8]. Although our regression model was adjusted by case definition and we only categorised case definitions into two groups, variation between studies may still result from inconsistent case definitions used in different studies. Our regression model could not be adjusted by serogroup due to very limited serogroup data for each age group. Although we only included papers published after 2000, the enrolment period still spanned from 1974 to 2015 for included studies. The decade of study was not statistically significant in our initial regression model, which may support previous research [48,74] and confirm CFR has not significantly decreased despite improvements in diagnostic techniques, clinical management and healthcare access. This is likely to be due to the pathophysiology of the disease process with an overwhelming effect of the cytokine storm limiting effectiveness of current treatment strategies.

We aimed to estimate CFR with minimum bias by searching publications and grey literature, contacting authors for additional information, and not restricting our search to developed countries. However, national surveillance networks are well established in developed countries, but very little data were identified from developing countries in Asia and South America. Countries with high endemic rates of IMD in Africa often reported mortality data associated with meningococcal meningitis only. Those studies were not included in this review as per the inclusion and exclusion criteria. The CFRs may be generally underestimated, as timely, reliable, and affordable health services may not be available in some countries especially in remote areas, which could substantially increase mortality from IMD [9]. Also, sudden deaths caused by IMD without hospitalisation were not considered in most studies. As notification or hospital discharge data were usually

used to identify IMD cases, those studies only included IMD patients who were admitted to hospital. Goldacre et al. found 616 deaths with meningococcal disease as a cause on the death registration record but those deaths did not have a corresponding hospital admission in a UK study [43]. During the same study period, 940 deaths occurred within 30 days after hospital admissions. The true mortality rate of IMD might be much higher than we estimated. A large proportion of CFR data were collected in young children aged less than 5 years. The concentration of data on this age group is likely to be due to the incidence peaking in young children. Only articles published in English were included which may result in publication bias. Historically N. meningitidis serogroup A has been the cause of the epidemics in the meningitis belt of sub-Saharan Africa. Since eligible studies in our review were conducted in non-African countries, the number of studies reporting MenA cases was small and most studies only enrolled one or two patients. Therefore, the meta-analysis was not performed for serogroup A related disease.

CONCLUSIONS

Despite those limitations and differences between countries, our review explored factors influencing CFR and emphasised the importance of age and serogroup as key factors determining CFRs by using different meta-analytic techniques. Our meta-analyses can provide clear, informative and contemporary results, advance our understanding of the disease burden and epidemiology of IMD, and assist in evaluating the potential benefits of new meningococcal vaccine programs.

AUTHOR CONTRIBUTION: BW, HM, LG and HHAA conceived and designed the study. BW conducted the searches. BW and RS extracted data and performed critical appraisal. HM and LG resolved divergencies. BW prepared the first draft of the manuscript under the direct supervision of HM, LG and HHAA. HM, RS, LG, and HHAA contributed to, reviewed and edited the manuscript.

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CONFLICT OF INTEREST: HM is an investigator on clinical trials of investigational vaccines sponsored by Industry. Her institution receives funding from Industry (GSK, Pfizer, Novavax) for Investigator led research. She does not receive any personal payments from Industry. There are no other conflicts of interest to declare.

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REFERENCES

1. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010; 10(12): 853-61.

2. Edge C, Waight P, Ribeiro S, Borrow R, Ramsay M, Ladhani SN. Clinical diagnoses and outcomes of 4,619 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: linkage analysis of multiple national databases. J Infect 2016;73(5):427-436.

3. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2016 – Invasive meningococcal disease (2014 data). https://ecdc.europa.eu/en/publications-data/invasive-meningococcal-disease-annual-epidemiological-report-2016-2014-data (accessed 25 July 2017).

4. MacNeil JR, Blain AE, Wang X, Cohn AC. Current Epidemiology and Trends in Meningococcal Disease-United States, 1996-2015. Clin Infect Dis 2018;66(8):1276-1281.

5. Martin NV, Ong KS, Howden BP, et al. Rise in invasive serogroup W meningococcal disease in Australia 2013-2015. Commun Dis Intell Q Rep 2016; 40(4): E454-E9.

6. Whittaker R, Dias JG, Ramliden M, et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004-2014. Vaccine 2017; 35(16): 2034-41.

7. Martinon-Torres F. Deciphering the Burden of Meningococcal Disease: Conventional and Under-recognized Elements. J Adolesc Health 2016; 59(2 Suppl): S12-20.

8. Sridhar S, Greenwood B, Head C, et al. Global incidence of serogroup B invasive meningococcal disease: a systematic review. Lancet Infect Dis 2015; 15(11): 1334-46.

9. Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther 2013; 11(6): 597-604.

10. Baccarini C, Ternouth A, Wieffer H, Vyse A. The changing epidemiology of meningococcal disease in North America 1945-2010. Hum Vaccin Immunother 2013; 9(1): 162-71.

11. Strifler L, Morris SK, Dang V, et al. The Health Burden of Invasive Meningococcal Disease: A Systematic Review. J Pediatric Infect Dis Soc 2016; 5(4): 417-30.

12. Wang B, Santoreneos R, Afzali H, Giles L, Marshall H. Costs of Invasive Meningococcal Disease: A Global Systematic Review. Pharmacoeconomics 2018; 36(10): 1201-1222.

13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.

14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283(15): 2008-12.

15. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2016 edition. Australia: The Joanna Briggs Institute, 2016.

16. Bradburn MJ, Deeks JJ, Altman DG. Metan-an alternative meta-analysis command. Stata Technical Bulletin 1999; 8(44).

17. Perrocheau A, Taha MK, Levy-Bruhl D. Epidemiology of invasive meningococcal disease in France in 2003. Euro Surveill 2005; 10(12): 238-41.

18. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ, 2014; 348: g2301.

19. Harrell F. General Aspects of Fitting Regression Models. Regression Modelling Strategies. New York: Springer, 2001.

20. Daures M, John M, Balter CV, et al. Relationships Between Clinico-Epidemiological Patterns of Invasive Meningococcal Infections and Complement Deficiencies in French South Pacific Islands (New Caledonia). J Clin Immunol 2015; 35(1): 47-55.

21. Ben-Shimol S, Dagan R, Schonmann Y, et al. Dynamics of childhood invasive meningococcal disease in Israel during a 22-year period (1989-2010). Infection 2013; 41(4): 791-8.

22. Husain EH, Barakat M, Al-Saleh M. Trends and variations in the epidemiology of meningococcal disease in Kuwait 1987-2013. J Infect Public Health 2015; 8(5): 441-7.

23. Memish Z, Al Hakeem R, Al Neel O, Danis K, Jasir A, Eibach D. Laboratory-confirmed invasive meningococcal disease: effect of the Hajj vaccination policy, Saudi Arabia, 1995 to 2011. Euro Surveill 2013; 18(37).

24. de Greeff SC, de Melker HE, Schouls LM, Spanjaard L, van Deuren M. Pre-admission clinical course of meningococcal disease and opportunities for the earlier start of appropriate intervention: a prospective epidemiological study on 752 patients in the Netherlands, 2003-2005. Eur J Clin Microbiol Infect Dis 2008; 27(10): 985-92.

25. Knol MJ, Hahné SJ, Lucidarme J, et al. Temporal associations between national outbreaks of meningococcal serogroup W and C disease in the Netherlands and England: an observational cohort study. Lancet Public Health 2017; 2(10): e473-e82.

26. Ladhani SN, Flood JS, Ramsay ME, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. Vaccine 2012; 30(24): 3710-6.

27. Ladhani SN, Lucidarme J, Newbold LS, et al. Invasive meningococcal capsular group Y disease, England and Wales, 2007-2009. Emerg Infect Dis 2012; 18(1): 63-70.

28. Montero JM, Prieto RG, Alejandre CG, Meca LA, Portugal P, de Miguel AG. Hospital admissions for meningococcal infection in Spain (1997-2005). J Infect 2009; 58(1): 15-20.

29. Piscopo T, Mallia-Azzopordi C, Grech V, Muscat M, Attard-Montalto S, Mallia C. Epidemiology and prognostic factors in meningococcal disease in a small island population: Malta 1994-1998. Eur J Epidemiol 2000; 16(11): 1051-6.

30. Steindl G, Liu YL, Schmid D, Orendi U, Kormann-Klement A, Heuberger S. Epidemiology of invasive meningococcal disease in Austria 2010. Wien Klin Wochenschr 2011; 123 Suppl 1: 10-4.

31. Roed C, Omland LH, Engsig FN, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. PLoS One 2010; 5(3): e9662.

32. McDonald EJ, F.; Reyholds, A.; Denham, B.; Smith-Palmer, A.; Edwards, G.; Cameron, C.;. The epidemiology of invasive meningococcal disease serogroup B in Scotland, 1999-2013. ESPID. Dublin, Ireland; 2014 (abstr).

33. Archer BN, Chiu CK, Jayasinghe SH, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999–2015: priority populations for vaccination. Med J Aust 2017; 207(9): 382-7.

34. Baker MG, Martin DR, Kieft CE, Lennon D. A 10-year serogroup B meningococcal disease epidemic in New Zealand: descriptive epidemiology, 1991-2000. J Paediatr Child Health 2001; 37(5): S13-9.

35. Brotherton J, McIntyre P, Puech M, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2001 to 2002. Commun Dis Intell Q Rep 2004; 28(Suppl 2): S41-S5.

36. Brotherton J, Wang H, Schaffer A, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. Commun Dis Intell Q Rep 2007; 31: S1.

37. Chiu C, Dey A, Wang H, et al. Vaccine preventable diseases in Australia, 2005 to 2007. Commun Dis Intell Q Rep 2010; 34: S1.

38. Cizman M, Gubina M, Paragi M, Beovic B, Lesnicar G. Meningococcal disease in Slovenia (1993-1999): serogroups and susceptibility to antibiotics. Slovenian Meningitis Study Group. Int J Antimicrob Agents 2001; 17(1): 27-31.

39. Darton T, Guiver M, Naylor S, et al. Severity of meningococcal disease associated with genomic bacterial load. Clin Infect Dis 2009; 48(5): 587-94.

40. Davison KL, Ramsay ME, Crowcroft NS, et al. Estimating the burden of serogroup C meningococcal disease in England and Wales. Commun Dis Public Health 2002; 5(3): 213-9.

41. Dey A, Knox S, Wang H, Beard FH, McIntyre PB. Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008-2011. Commun Dis Intell Q Rep 2016; 40 Suppl: S1-70.

42. Gil-Prieto R, Garcia-Garcia L, Alvaro-Meca A, Gonzalez-Escalada A, Viguera Ester P, Gil De Miguel A. The burden of hospitalizations for meningococcal infection in Spain (1997-2008). Vaccine 2011; 29(34): 5765-70.

43. Goldacre MJ, Maisonneuve JJ. Mortality from meningococcal disease by day of the week: English national linked database study. J Public Health (Oxf) 2013; 35(3): 413-21.

44. Gottfredsson M, Diggle MA, Lawrie DI, et al. Neisseria meningitidis sequence type and risk for death, Iceland. Emerg Infect Dis 2006; 12(7): 1066-73.

45. Gottfredsson M, Reynisson IK, Ingvarsson RF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis 2011; 53(9): e117-24.

46. Gray SJ, Trotter CL, Ramsay ME, et al. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: contribution and experiences of the Meningococcal Reference Unit. J Med Microbiol 2006; 55(Pt 7): 887-96.

47. Hanquet GC, Agnew E, Trotter, et al. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study. Health Technology Assessment (HTA). 2014; KCE Reports 231.

48. Howitz M, Lambertsen L, Simonsen JB, Christensen JJ, Molbak K. Morbidity, mortality and spatial distribution of meningococcal disease, 1974-2007. Epidemiol Infect 2009; 137(11): 1631-40.

49. Knol MJ, Ruijs WL, Antonise-Kamp L, de Melker HE, van der Ende A. Implementation of MenACWY vaccination because of ongoing increase in serogroup W invasive meningococcal disease, the Netherlands, 2018. Euro Surveill 2018; 23(16).

50. Ladhani SN, Beebeejaun K, Lucidarme J, et al. Increase in endemic Neisseria meningitidis capsular group W sequence type 11 complex associated with severe invasive disease in England and Wales. Clin Infect Dis 2015; 60(4): 578-85.

51. McIntyre P, Gidding H, Gilmour R, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1999 to 2000. Commun Dis Intell Q Rep 2002; Suppl(2002 May): 32-6.

52. Muscat M, Spiteri G, Calleja N, et al. Invasive meningococcal disease in Malta: an epidemiological overview, 1994-2007. J Med Microbiol 2009; 58(Pt 11): 1492-8.

53. Parent du Chatelet I, Deghmane AE, Antona D, et al. Characteristics and changes in invasive meningococcal disease epidemiology in France, 2006-2015. J Infect 2017; 74(6): 564-74.

54. Parikh SR, Campbell H, Gray SJ, et al. Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015. Vaccine 2018; 36(26):3876-3881.

55. Ruedin HJ, Ninet B, Pagano E, Rohner P. Epidemiology of meningococcal disease in Switzerland, 1999-2002. Eur J Clin Microbiol Infect Dis 2004; 23(7): 517-22.

56. Sadarangani M, Scheifele DW, Halperin SA, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015; 60(8): e27-35.

57. Schrauder A, Claus H, Elias J, Vogel U, Haas W, Hellenbrand W. Capture-recapture analysis to estimate the incidence of invasive meningococcal disease in Germany, 2003. Epidemiol Infect 2007; 135(4): 657-64.

58. Shigematsu M, Davison KL, Charlett A, Crowcroft NS. National enhanced surveillance of meningococcal disease in England, Wales and Northern Ireland, January 1999-June 2001. Epidemiol Infect 2002; 129(3): 459-70.

59. Skoczynska A, Wasko I, Kuch A, et al. A decade of invasive meningococcal disease surveillance in Poland. PLoS One 2013; 8(8): e71943.

60. Squires SG, Deeks SL, Tsang RS. Enhanced surveillance of invasive meningococcal disease in Canada: 1 January, 1999, through 31 December, 2001. Can Commun Dis Rep 2004; 30(3): 17-28.

61. Squires SG, Pelletier L, Mungai M, Tsang R, Collins F, Stoltz J. Invasive meningococcal disease in Canada, 1 January 1997 to 31 December 1998. Can Commun Dis Rep 2000; 26(21): 177-82.

62. Stoof SP, Rodenburg GD, Knol MJ, et al. Disease Burden of Invasive Meningococcal Disease in the Netherlands Between June 1999 and June 2011: A Subjective Role for Serogroup and Clonal Complex. Clin Infect Dis 2015; 61(8): 1281-92.

63. Yezli S, Assiri AM, Alhakeem RF, Turkistani AM, Alotaibi B. Meningococcal disease during the Hajj and Umrah mass gatherings. Int J Infect Dis 2016; 47: 60-4.

64. Harrison LH. Prospects for vaccine prevention of meningococcal infection. Clin Microbiol Rev 2006; 19(1): 142-64.

65. Trotter CL, Fox AJ, Ramsay ME, et al. Fatal outcome from meningococcal disease--an association with meningococcal phenotype but not with reduced susceptibility to benzylpenicillin. J Med Microbiol. 2002;51(10):855-60.

66. Hahné SJ, Gray SJ, Jean-François, et al. W135 meningococcal disease in England and Wales associated with Hajj 2000 and 2001. Lancet. 2002;359(9306):582-3.

67. Whalen CM, Hockin JC, Ryan A, Ashton F. The changing epidemiology of invasive meningococcal disease in Canada, 1985 through 1992. Emergence of a virulent clone of Neisseria meningitidis. JAMA. 1995;273(5):390-4.

68. Mayer LW, Reeves MW, Al-Hamdan N, et al. Outbreak of W135 meningococcal disease in 2000: not emergence of a new W135 strain but clonal expansion within the electophoretic type-37 complex. J Infect Dis. 2002;185(11):1596-605.

69. Hart CA, Thomson AP. Meningococcal disease and its management in children. BMJ 2006; 333(7570): 685-90.

70. Cohn AC, MacNeil JR, Harrison LH, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. Clin Infect Dis 2010; 50(2): 184-91.

71. Gunaratnam P, Massey P, Durrheim D, Torvaldsen S. Invasive meningococcal disease in elderly people, New South Wales, Australia, 1993 to 2012. Western Pac Surveill Response J 2013; 4(4): 4-10.

72. Dale AP, Read RC. Genetic susceptibility to meningococcal infection. Expert Rev Anti Infect Ther. 2013;11(2):187-99.

73. Balding J, Healy CM, Livingstone WJ, et al. Genomic polymorphic profiles in an Irish population with meningococcaemia: is it possible to predict severity and outcome of disease? Genes Immun. 2003 Dec;4(8):533-40.

74. Goldacre MJ, Roberts SE, Yeates D. Case fatality rates for meningococcal disease in an English population, 1963-98: database study. BMJ 2003; 327(7415): 596-7.

Supplementary Table 1: Search strategies

PubMed		
Invasive Meningococcal Disease	Clinical and Economic Burden	Filters
meningococcal Infections [mh:noexp] OR Meningitis, Meningococcal [mh:noexp] OR Neisseria meningitidis [mh:noexp] OR Neisseria meningitidis [tiab] OR Meningococc* [tiab]	Case fatality [tiab] OR Complications[tiab] OR Sequela*[tiab] OR Outcome*[tiab] OR Mortality[mh] OR Mortalit*[tiab] OR Death rate* [tiab] OR Incidence*[tiab] OR Morbidity[mh] OR Morbidit*[tiab] OR Health status[mh] OR Health status[tiab] Costs and cost analysis[mh] OR Economics, Medical [mh] OR Fees, Medical[mh] OR Fees, Pharmaceutical[mh] OR Hospital Charges [mh] OR economics[sh] OR	English

	models, economic[mh] OR Economic*[tiab] OR Cost[tiab] OR Costs[tiab] OR Costing*[tiab] OR Burden[tiab] OR Hospitals/utilization[mh] OR Expenditure*[tiab]	
Embase		
Invasive Meningococcal Disease	Clinical and Economic Burden	
‘Meningococcosis’/syn OR Meningococc*:ab,ti OR ‘Neisseria meningitidis’/syn	'Case fatality':ti,ab OR Complication*:ti,ab OR Sequela*:ti,ab OR 'Treatment outcome'/syn OR Outcome*:ti,ab OR 'Mortality'/syn OR Mortalit*:ti,ab OR ‘Incidence’/syn OR Incidence:ti,ab OR 'Morbidity'/de OR Morbidity:ti,ab OR 'Disease course':ti,ab,de OR	(NOT [medline]/lim) AND [English]/lim

	Burden:ti,ab OR 'Health status':ti,ab,de OR 'Economic evaluation'/syn Cost*:ab,ti OR Economic* NEAR/5 (illness* OR medical OR model*) OR 'Health care utilization'/syn OR Utilization:ab,ti OR Utilisation:ab,ti OR Expediture*:ti,ab	
Cochrane		
Invasive Meningococcal Disease	Clinical and Economic Burden	
MeSH descriptor: [Meningococcal Infections] explode all trees OR MeSH descriptor: [Neisseria meningitidis] explode all trees OR MeSH descriptor: [[Meningitis, Meningococcal]] explode all trees OR	MeSH descriptor: [Disease Progression] explode all trees OR MeSH descriptor: [Morbidity] explode all trees OR MeSH descriptor: [Treatment Outcome] explode all trees OR	

Meningococcal:ti,ab,kw (Word variations have been searched)	MeSH descriptor: [Mortality] explode all trees OR “case fatality” OR “morbidity” OR “incidence” OR “sequelae” OR “clinical course " OR “complication*” OR “neurological” OR “deafness” or “seizure*” OR “outcome*”:ti,ab,kw (Word variations have been searched) MeSH descriptor: [Costs and Cost Analysis] explode all trees OR MeSH descriptor: [Models, Economic] explode all trees OR MeSH descriptor: [Economics, Hospital] explode all trees OR MeSH descriptor: [Economics, Medical] explode all trees OR	

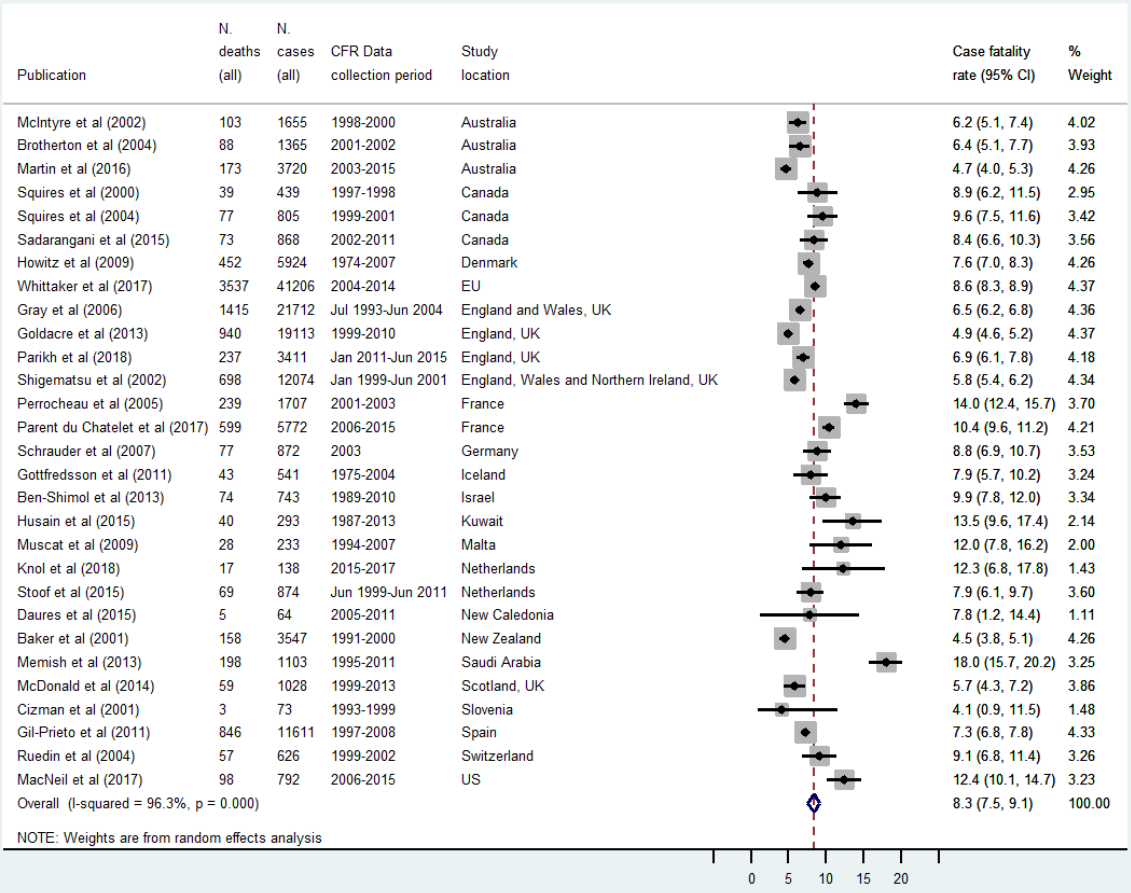
	MeSH descriptor: [Economics, Nursing] explode all trees OR MeSH descriptor: [Fees and Charges] explode all trees OR MeSH descriptor: [Health Resources] explode all trees and with qualifier(s): [Utilization - UT] OR “cost*” or “economic*” or "resource use" or "resource utilization" or "resource utilisation" or "direct and indirect cost":ti,ab,kw (Word variations have been searched)	

Supplementary Table 2: Estimates of CFR by age for laboratory confirmed IMD cases only

Age	Predicted CFR (%)	95%CI (%)
1	9.0	6.8-11.3
2	8.5	6.4-10.6
3	8.0	6.0-10.1
4	7.7	5.7-9.6
5	7.3	5.5-9.2
6	7.1	5.3-9.0
7	7.0	5.2-8.9
8	7.1	5.2-8.9
9	7.2	5.3-9.1
10	7.4	5.5-9.4
11	7.8	5.8-9.7
12	8.2	6.1-10.2
13	8.6	6.5-10.8
14	9.2	6.9-11.5
15	9.8	7.4-12.2
16	10.4	7.8-12.9
17	11.0	8.3-13.6
18	11.5	8.7-14.3
19	12.1	9.2-15.0
20	12.6	9.6-15.6
21	13.0	9.9-16.1
22	13.4	10.2-16.6
23	13.8	10.5-17.1
24	14.1	10.8-17.5
25	14.4	11.0-17.8
26	14.7	11.2-18.1
27	14.9	11.4-18.4
28	15.0	11.5-18.6
29	15.2	11.7-18.7
30	15.3	11.7-18.8
31	15.4	11.8-18.9
32	15.4	11.9-19.0
33	15.5	11.9-19.1
34	15.5	11.9-19.1
35	15.5	11.9-19.1
36	15.5	12.0-19.1
37	15.5	12.0-19.1
38	15.5	12.0-19.1
39	15.6	12.0-19.1
40	15.6	12.0-19.2
41	15.6	12.0-19.2
42	15.7	12.0-19.3
43	15.7	12.1-19.3

Age	Predicted CFR (%)	95%CI (%)
44	15.8	12.2-19.5
45	15.9	12.3-19.6
46	16.1	12.4-19.8
47	16.2	12.5-19.9
48	16.4	12.6-20.2
49	16.6	12.8-20.4
50	16.8	13.0-20.6
51	17.0	13.2-20.9
52	17.3	13.4-21.2
53	17.6	13.6-21.5
54	17.9	13.8-21.9
55	18.2	14.1-22.3
56	18.5	14.4-22.7
57	18.9	14.7-23.1
58	19.3	15.0-23.5
59	19.7	15.3-24.0
60	20.1	15.7-24.5
61	20.5	16.1-25.0
62	21.0	16.5-25.5
63	21.5	16.9-26.1
64	22.0	17.3-26.6
65	22.5	17.8-27.2
66	23.1	18.2-27.9
67	23.6	18.7-28.5
68	24.2	19.2-29.2
69	24.8	19.8-29.9
70	25.5	20.3-30.6
71	26.1	20.9-31.3
72	26.8	21.5-32.1
73	27.5	22.1-32.9
74	28.2	22.7-33.7
75	28.9	23.3-34.5
76	29.6	24.0-35.3
77	30.4	24.6-36.2
78	31.2	25.3-37.1
79	32.0	26.0-37.9
80	32.8	26.7-38.8

Supplementary Figure 1: Forest plot for the overall CFR



3.1.2 SEQUELAE ASSOCIATED WITH MENINGOCOCCAL DISEASE

The burden of IMD was systematically reviewed (See Appendix: IMD systematic review protocol) including mortality and sequelae. In the previous section, the mortality due to IMD was reviewed and quantitatively synthesised. Published evidence of sequelae associated with IMD was systematically reviewed and presented in this section. With earlier diagnosis and prompt treatment, outcomes for most IMD patients are good. However, IMD can cause permanent and devastating disabilities. Viner et al found 9% of children infected with MenB had potentially lifelong deficits such as severe cognitive disabilities, seizures, hearing loss, motor impairment, visual loss, or major communication disability [98]. Symptoms of fatigue and headache may persist for months after acute illness [96]. Up to 58% of adolescents had minor and major sequelae following the disease [22].

Most commonly reported sequelae are arthritis, chronic migraine, neurocognitive sequelae, hearing loss, seizures/epilepsy, speech and communication problems, and amputation. As the definition of sequelae, serogroups of the disease, follow-up period, study population and study design varied significantly across studies, published evidence of sequelae/complications associated with IMD were not quantitatively synthesised. Furthermore, the quality of healthcare services in different countries may impact the outcomes of the disease. Results derived from studies with small sample sizes often produce wide variance [99]. Therefore, only studies conducted in developed countries with large sample sizes are discussed here.

Neurocognitive sequelae

Hearing loss, vision impairments, seizures

Those sequelae were often reported separately in the literature. Hearing loss, impairments or deficits were observed in 1.9% [100] - 12.9% [101] of IMD patients. IMD patients were interviewed 1 - 3 years post infection in a UK study. There were 65 out of 504 (12.9%) patients stating they had sustained hearing loss [101]. By searching ICD codes relevant to hearing loss, a Danish study found 44 of 2286 (1.9%) IMD patients experienced hearing loss [100]. In a case-control study (MOSAIC), pure tone audiometric tests were performed for children infected with MenB disease and controls [98]. It was found that 15/232 cases (6.5%) and 4/318 controls (1.3%) had hearing loss ≥20 db. Blindness or visual impairments were reported in 0.3% [102] - 8.7% [101] of IMD patients. The MOSAIC study identified 1/239 (0.4%) had registered blindness with no blindness in controls [98]. Darton et al reported that the percentage of self-reported vision impairment was 44/506 (8.7%) [101]. The rates of self-perceived hearing/vision impairments are much higher than the rates of impairments documented in medical records or detected in the studies.

It was estimated that 0.6% [103] - 13.9% [104] of IMD patients had seizures/epilepsy. In a retrospective study conducted in Iceland, epilepsy was less common (3/541; 0.6%) than either hearing loss (14/541; 2.6%) or renal failure (15/541; 2.8%) [103]. However, two US studies that employed searches of ICD codes reported epilepsy/seizure was one of the most common complications associated with IMD, with seizures (11.7% [105] - 13.9% [104]) and epilepsy (5.8% [104] - 7.0% [105]) affecting notable proportions of patients.

Other neurocognitive impairments

Depending on definitions of neurocognitive sequelae, sample sizes, study population and study design, the rates of other neurocognitive impairments varied between 1.7% [106] and 10.9% [107], including brain injuries [102,106], motor deficits/motor disabilities

[12,22,102,107], impaired muscle functions [108], brain nerve damage [108], paresthesia [108], developmental delay [109], etc. Chronic migraine (0.6% [103] - 4.6% [97]) was also reported in two studies through medical note review [96,103].

Musculoskeletal sequelae

Amputation following septicaemia was observed in 1 - 3% of IMD patients. The severity of amputation ranged from digit amputation to multiple limb amputation. The rate of multiple limb amputation was less frequent (0.5% [102] - 0.8% [110]). Limb deficiency/deformities were often reported in children with meningococcal septicaemia or septic shock [12,111-113]. Lower limb-length discrepancy occurred in 7 of 120 (6%) children with meningococcal septic shock [112]. It was also reported that 16 of 122 children (13.1%) with meningococcal septicaemia experienced physeal growth arrests [113]. Almost ten percent of IMD patients experienced arthritis. Although all patients recovered, some of them required long-term steroid treatment [114].

Dermatological sequelae

Skin scars with or without graft resulting from skin necrosis were commonly reported in the literature. Depending on the method of identification (through medical note review or ICD code search) and definition of skin scarring (with or without grafting), the sequelae rate of skin scarring ranged from 0.9% [108] - 18.0% [102].

Renal sequelae

Bettinger et al found that children (3.6%) were significantly less likely to experience renal dysfunction compared with adults (33%), which may explain a lower proportion of renal impairment observed in paediatric patients [96,109]. The frequency of renal sequelae

including renal dysfunction, acute renal failure, chronic renal failure and renal insufficiency have been reported from 0.4% [115] to 8.7% [104].

Psychological sequelae

In a qualitative study, one patient recalled that when he was sent to the intensive care unit, all of his father's hair went grey overnight because of the sudden stress of his child having a life-threatening infection [116]. However, limited research has been conducted to assess the psychological impact of IMD in patients [98,106,117-119] and their families [120]. In the Netherlands, Vermunt et al assessed psychological and behavioural problems in paediatric patients with septic shock [117-119]. Their study results indicated the younger the child at the time of the disease, the more problems were reported by their patients after four years following the infection [118]. Scars were a significant predictor of unfavourable outcomes on social acceptance or close friendship [119]. Anxiety disorders (e.g. generalised anxiety disorder, social phobia, separation anxiety disorder), post-traumatic stress disorder, behavioural and emotional disorders (oppositional defiant disorder, conduct disorder) and attention deficit hyperactivity disorder (ADHD) have been reported in those studies. ADHD was also reported to be potentially associated with bacterial meningitis [121]. Fellick et al reported three cases (2.6%) and one control were formally diagnosed with ADHD by using Connor's Rating Scales–Revised assessment tool [106]. Viner et al identified ADHD at 50% probability or more in 17 cases (11.4%) and 4 controls by using a development and wellbeing assessment tool [98]. A diagnosis of ADHD can be controversial and cannot be made with a single tool or test. In the research setting, the percentage of real ADHD cases may be subject to uncertainties in the psychological tools/criteria used.

Summary

Devastating long-term disabilities can result from IMD. However, this systematic review found most patients were followed up less than five years in the included studies. Psychological problems caused by the acute infection and long-term disabilities may be under-recognised in patients and their family members. Diversity in sample size, study population, follow-up period, data collection methods, and definition of sequelae may be partly responsible for the significant heterogeneity in study results. For example, the rate of patient-perceived hearing loss is much higher than the rate of hearing loss confirmed by audiology tests during the study. Only a very limited number of studies prospectively followed patients and performed hearing, psychological, or neurocognitive tests. The MOSAIC study provided informative estimates of the range of disabilities experienced by children who had MenB. Since the incidence of MenW disease has continuously increased, the serogroup-specific study results may not be representative of contemporary patterns. It was reported that patients with MenB disease had less severe outcomes than those with MenC disease [102,103]. Data on MenB disease burden may underestimate disability outcomes caused by IMD in general or compared to other serogroups.

3.1.3 COSTS OF MENINGOCOCCAL DISEASE

IMD is associated with an increased risk of disabilities in young children and adolescents. A systematic review was performed to estimate the burden of IMD including the costs and resource use associated with IMD. Results in regard to IMD costs and resource use published in the journal “PharmacoEconomics”, are presented in Section 3.1.3.2.

3.1.3.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Costs of Invasive Meningococcal Disease: A Global Systematic Review
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Wang B, Santoreneos R, Haji Ali Afzali H, Giles L, Marshall H. Costs of Invasive Meningococcal Disease: A Global Systematic Review. PharmacoEconomics 2018; 36(10):1201-1222

Principal Author

Name of Principal Author (Candidate)	Bing Wang		
Contribution to the Paper	BW conceived and designed the study, conducted database searches, extracted, analysed and interpreted data, performed quality assessment, and produced the first draft of the manuscript.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Renee Santoreneos		
Contribution to the Paper	RS extracted data, performed quality assessment, and reviewed the manuscript.		
Signature		Date	18/10/18

Name of Co-Author	Hossein Haji Ali Afzali		
Contribution to the Paper	HHAA conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/2018

Name of Co-Author	Lynne Giles		
Contribution to the Paper	LG conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/18

Name of Co-Author	Helen Marshall		
Contribution to the Paper	HM conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	04 OCT 2018

Please cut and paste additional co-author panels here as required.

3.1.3.2 PUBLICATION

PharmacoEconomics
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SYSTEMATIC REVIEW

Costs of Invasive Meningococcal Disease: A Global Systematic Review

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Abstract

Background Invasive meningococcal disease remains a public health concern because of its rapid onset and significant risk of death and long-term disability. New meningococcal serogroup B and combination serogroup ACWY vaccines are being considered for publicly funded immunization programs in many countries. Contemporary costing data associated with invasive meningococcal disease are required to inform cost-effectiveness analyses.

Objective The objective of this study was to estimate costs and resource utilization associated with acute infection and the long-term care of invasive meningococcal disease.

Data Sources and Methods PubMed, EMBASE, The Cochrane Library, health economic databases, and electronically available conference abstracts were searched. Studies reporting any costs associated with acute infection and long-term sequelae of invasive meningococcal disease in English were included. All costs were converted into purchasing power parity-adjusted estimates [international dollars (I$)] using the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter.

Results Fourteen studies met our eligibility criteria and were included. The mean costs of acute admission ranged from I$1629 to I$50,796, with an incremental cost of I$16,378. The mean length of hospital stay was reported to be 6–18 days in multiple studies. The average costs reported for readmissions ranged from I$7905 to I$15,908. Key variables such as the presence of sequelae were associated with higher hospitalization costs and longer inpatient stay. No studies estimated direct non-healthcare costs and productivity loss. Ten studies reported only unadjusted mean values without using appropriate statistical methods for adjustment.

Conclusions Invasive meningococcal disease can result in substantial costs to healthcare systems. However, costing data on long-term follow-up and indirect costs used to populate health economic models are lacking.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-018-0679-5) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

Invasive meningococcal disease (IMD) is a public health concern worldwide. Assumption and expert opinions have been commonly used in health economic evaluations to estimate unit costs associated with acute admission and long-term care of IMD.

We systematically reviewed and synthesized published evidence of costs and resource utilization relevant to acute infection and long-term sequelae of IMD. The average healthcare costs of acute infection ranged from I$1629 in Colombia to I$50,796 in USA with an incremental cost of I$16,378.

The public health burden of the disease is substantial with significant increases in healthcare costs and resource use for meningococcal patients with sequelae.

1 Introduction

Although the incidence of invasive meningococcal disease (IMD) is relatively low in high-income countries, the disease still causes public health concern and anxiety because of its rapid onset, an increased risk of mortality in adolescents, and high rates of severe sequelae in children [1–4]. Results from retrospective and prospective studies show almost 40% of children had sequelae following IMD infection [2, 5]. Major disabling deficits including amputation, deafness, epilepsy, and learning difficulties were identified in around 10% of pediatric survivors [2]. Among 13 known serogroups, serogroups A, B, C, W, and Y are responsible for most cases of IMD with serogroup X mainly causing disease in Africa [6]. Vaccines against serogroup B disease (MenB), which causes around 40–85% of cases in Australia [7, 8], 64% of cases in Europe [9], and almost 50% in USA [10], have recently been developed. However, the MenB vaccination is publicly funded in a limited number of countries. The recommendation of funding the MenB vaccine under the National Immunisation Program Schedule in Australia has been rejected three times by the Pharmaceutical Benefits Advisory Committee, mainly owing to uncertainty around evidence on the effectiveness of the vaccine and potential for herd immunity response [11–13]. Although initially rejected in the UK [14], the Joint Committee on Vaccination and Immunisation (JCVI) finally recommended inclusion of the MenB vaccine into the UK immunization schedule at a 'cost-effective' price, which was significantly lower than the list price for the MenB vaccine [15]. Changes such as adding litigation costs to the final analysis supported the cost effectiveness of a MenB vaccination program in infants. The JCVI also noted that a similar model with key differences in a number of important parameters including healthcare resources could reach different conclusions on cost effectiveness when comparing an independent study with another unpublished cost-effectiveness study [14]. Because direct and indirect costs associated with acute treatment and long-term care in patients with IMD are important inputs into cost-effectiveness models, detailed costing data are required to inform cost-effectiveness analyses. The paucity of costing data and its potential impact on cost-effectiveness analyses have been acknowledged in recent economic evaluations of the MenB vaccine [16, 17].

By assessing the direct and indirect costs of a particular condition, the results of cost-of-illness (COI) studies can be used to inform public funding decisions such as estimating the magnitude of costs that can potentially be saved by preventative programs (e.g., MenB vaccination). Cost-of-illness studies have also been frequently cited to attract public attention to specific health problems by describing their impact on healthcare resources and productivity loss [18].

To our knowledge, no systematic reviews have been performed to estimate the financial impact associated with acute treatment and long-term follow up of IMD. Anonychuk et al. systematically reviewed the costs related to containment strategies for IMD outbreaks and concluded that the outbreaks result in substantial disruption and costs to society [19]. In a review article, Martinón-Torres delineated the extensive clinical and economic burden of IMD including the overlooked family burden, legal costs, and adaptive measures required for IMD survivors with disabilities [20]. However, this narrative review was based mainly on the author's experience and knowledge, without a description of the literature searching methodology. This review article also used several costing studies related to all-cause bacterial meningitis including pneumococcal and other causes of meningitis to outline the financial burden of IMD.

The aim of the present study is to provide a systematic review of the global evidence on direct or indirect costs of IMD published since 2000. In addition, we compared methodologies used in each study and summarized the key factors affecting healthcare costs.

2 Methods

2.1 Literature Search

A search of the literature was conducted using the electronic databases: PubMed, EMBASE, The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effectiveness. The search terms included combinations of Medical Subject Headings/ Emtree and text words contained in the title and abstract. Details on search strategies are presented in Table 1 of the Electronic Supplementary Material (ESM). Only studies reporting costing results are included in this review (Fig. 1). Health economic databases were also searched, including the Health Economic Evaluation Database, Cost-effectiveness Analysis Registry, Health Technology Assessment Database, and the Paediatric Economic Database Evaluation. Gray literature available online was

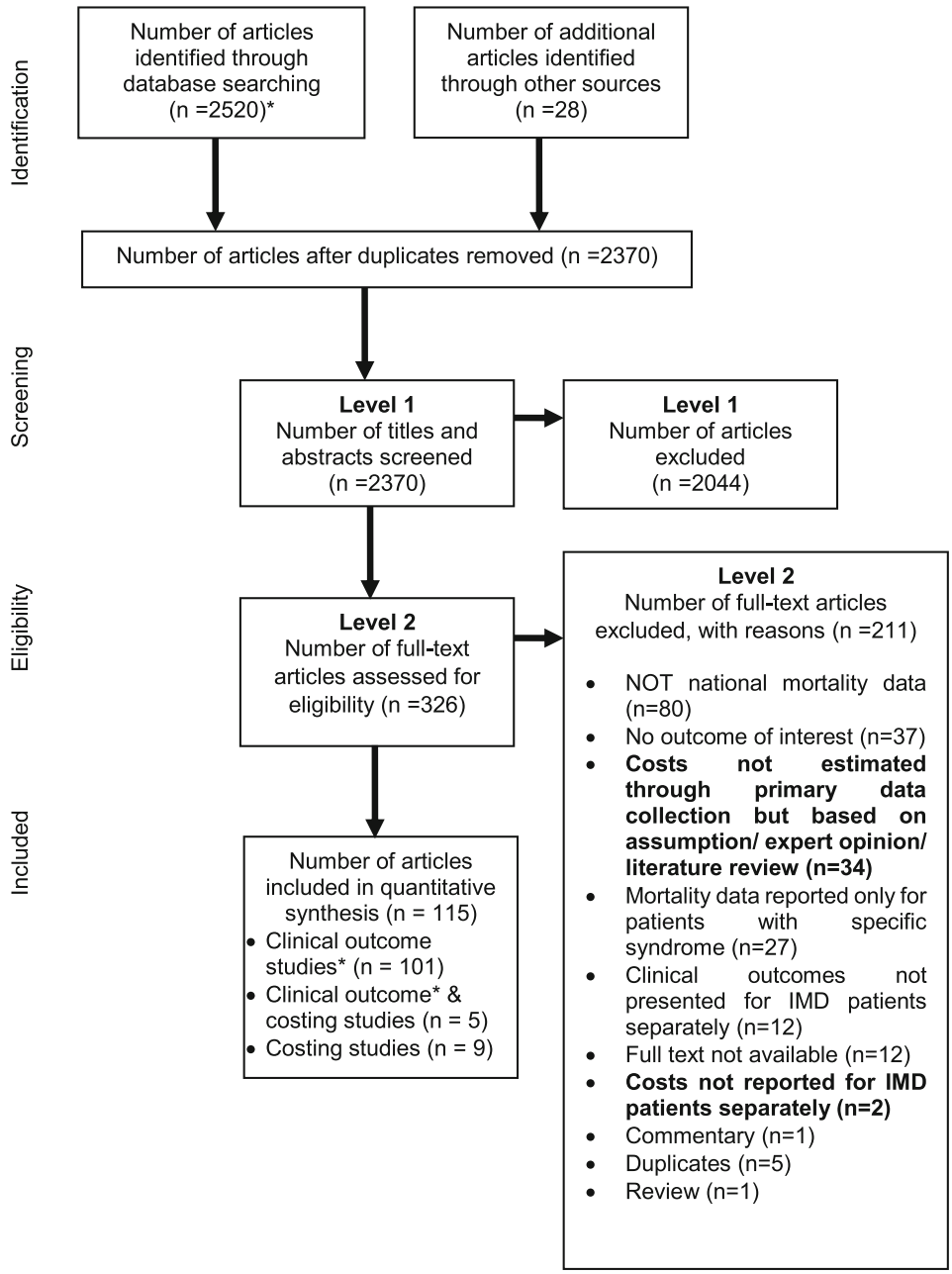

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for article inclusion and exclusion. *IMD* invasive meningococcal disease

* The systematic review covered clinical outcomes and financial costs of IMD. Only the results of costing studies are presented here.

searched for relevant abstracts and/or posters from the following organizations: Meningitis Research Foundation, Infectious Diseases Society of America, International Pathogenic Neisseria Conference, European Society for Paediatric Infectious Diseases, International Congress on Infectious Diseases, World Society for Pediatric Infectious Diseases, and the Australian Society for Infectious Diseases. If conference abstracts were eligible at the title and abstract screen, the first authors were contacted by e-mail and detailed study information was sought. The reference lists of eligible articles and other relevant review articles [19, 20] were searched for additional studies. The search was conducted by one reviewer (BW) from August 2016 to September 2017.

2.2 Inclusion and Exclusion Criteria

The article selection process occurred in two phases: (1) citation screen: titles and abstracts of articles identified from the electronic databases and from Internet searches were reviewed; and (2) full-text screen: the full text of articles selected at the citation screen were obtained and reviewed for eligibility. One reviewer (BW) completed the screening process according to a predefined protocol.

Studies were eligible if direct and/or indirect costs associated with acute infection and long-term complications/sequelae of IMD were reported through primary data collection. We excluded studies only recruiting patients with IMD as part of a larger population but not presenting outcomes for the IMD group separately. Comments, letters, editorials, case reports (fewer than ten patients with IMD), and reviews were excluded. Because the first national meningococcal vaccination (meningococcal C vaccines) program was implemented in the UK in 1999, we expected the vaccination could make significant changes to the epidemiology of IMD. Therefore, the search was restricted to studies published after January 2000. Studies reported in languages other than English were excluded.

Reporting and performing this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 statement [21]. The inclusion and exclusion processes were documented.

2.3 Data Extraction and Quality Assessment

Data were independently extracted by two reviewers (BW and RS) using predefined data fields. Data extracted were: direct and indirect costs, and healthcare resource utilization [e.g., length of hospital stay (LOS), frequency of outpatient services and readmissions], study design, funding, study location, study population (e.g., sample size, serogroup, and age at illness), perspective, data sources, cost items, model type, time horizon, discount rates, cost adjustment approaches, sensitivity analysis, statistical methods, and limitations considered by authors.

As there are no consensus agreement or validated guidelines explicitly designed to perform critical appraisal for the COI studies, the quality of included studies was assessed using a checklist (Table 2 of the ESM), which was developed on the basis of the Drummond 10-point Checklist [22], the International Society For Pharmacoeconomics and Outcomes Research checklist for retrospective database studies [23], and criteria used in previous COI systematic reviews [24–28]. Two independent reviewers (BW and RS) assessed the quality of the studies and any divergences between reviewers were resolved by discussion.

No studies fulfilled all criteria, as most studies were only conducted from the healthcare system or third-party payer perspective without covering all relevant perspectives, used national hospital discharge or insurance claim databases with no description of data reliability and validity, or reported mean values with no adjustment for confounding variables.

2.4 Data Synthesis

To compare costing data across heterogeneous studies, all cost estimates were converted into international dollars using purchasing power parity according to the recommended guideline [22] and similar studies in the literature [29–31]. Henceforth, all cost estimates are presented with the sign of I$. The purchasing power parity-adjusted estimates were calculated using the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter [32]. Because the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre cost converter requires cost estimates reported in the original study's local currency for inflation adjustment, the cost estimates were converted back into the local currency for studies not reporting their results in the study country's local currency but in US$. If the exchange rate was not presented in the article, the average exchange rate (according to OANDA historical exchange rates [33]) for the reported year was used. If the price year was not specified in the publication, the last year of the study period was utilized. All costs were adjusted to the year 2014, as that was the last price year reported in the included studies.

A meta-analysis was performed using the metaan ado package [34] in STATA 14.2 (StataCorp LLC., College Station, TX, USA) [35]. Owing to marked variation in data sources, age group, follow-up period, cost items, statistical methods, and confounder adjustment across studies, a significantly high level of heterogeneity (I^2 = 96.61%,

$\tau^2 = 4.6 \times 10^8$) was found in the pooled estimate of unadjusted acute admission costs. Owing to the considerable heterogeneity demonstrated in the meta-analysis, only descriptive results are presented here.

3 Results

3.1 Overview of Studies

The search strategy identified 2370 studies that met the inclusion criteria (Fig. 1). After title and abstract screening, full manuscripts of 326 articles were reviewed so as to exclude additional articles. Among 115 articles retained to assess the clinical and financial burden of IMD, 14 articles reported costing results (Table 1). The majority of the studies were conducted in high-income countries, including six studies in USA, two in Spain, one in Belgium, one in Italy, and another study in Australia. Three studies reported costs associated with IMD outbreaks in the UK, Colombia, and Brazil.

3.2 Methodological Heterogeneity

Although all studies were conducted from the perspective of the healthcare system or third-party payers with a bottom-up approach, the range of cost items included in each study varied considerably (Table 2). Except for three outbreak studies, all other studies used retrospective insurance claim or hospital discharge databases. Five studies did not provide detailed cost breakdowns with three of them reporting costs based on Diagnosis Related Group codes [36, 38, 41, 45, 48]. Five studies provided a breakdown of healthcare costs by age groups. The main cost item reported was inpatient costs. Some studies also included other cost components such as emergency department, hospital outpatient services, physician office visits, nursing home services and rehabilitation facilities, pharmacy claims, and associated costs. Cost adjustment was not documented in three studies [36, 41, 45]. One study compared costing data and resource utilization between cases and controls [38]. Four studies reported healthcare costs relevant to medical follow-up after hospital discharge [39, 40, 43, 49]. The follow-up period varied between 0 and 3659 days. Serogroup information was only available for six studies.

Only four studies used statistical models to adjust cost and resource utilization data [38, 39, 43, 49]. Among those, a generalized linear model was commonly used for costing data adjustment, with three studies fitting a generalized linear model with a log link function and a gamma distribution. Resource utilization was analyzed using negative binomial regression, Cox proportional hazard, or Poisson regression models. Two studies chose the same set of confounding variables [39, 43]. There is considerable variability in selecting confounding variables between the aforementioned two studies and other studies. Both unadjusted and adjusted analyses were presented in three studies [39, 43, 49]. Except for patients without sequelae in two US studies, all adjusted costs were reported to be lower than unadjusted costs. For those performing only unadjusted analyses, four of them presented mean and/or median values with no variability measures (e.g., range, interquartile range, 95% confidence interval or standard deviation) [40, 41, 45, 46].

3.3 Direct Medical Cost Estimates and Healthcare Resource Utilization

The unadjusted acute admission costs per patient ranged from I$1629 in Colombia [47] to I$50,796 in USA [39] (Tables 3, 4). The unadjusted mean cost of follow-up care during 1-year post-admission was reported as I$23,565 in USA including readmission costs and other healthcare expenses [40]. The unadjusted total healthcare cost for initial admission, readmissions, and other healthcare services was around I$60,000 on average in USA during 1-year post-admission [39, 40, 43]. Readmissions resulted in I$15,908 in USA [40] and I$7905 in Australia [49] in unadjusted analyses with varied follow-up periods. The adjusted mean costs associated with acute admission were reported in four studies ranging from I$8571 in Australia [49] to I$23,792 in USA [38]. The adjusted mean cost relevant to IMD readmissions was estimated to be I$935 in Australian pediatric patients with sequelae [49]. Both unadjusted and adjusted healthcare costs including inpatient costs almost doubled in patients with sequelae compared with patients without sequelae [38, 43, 49]. The incremental cost and LOS of acute admission (I$16,378, 4.3 days) could only be inferred from a case-control study [38].

Of the 14 included studies, ten reported an estimated hospital resource use. The mean LOS during acute admission was reported from 8 to 18 days in unadjusted analyses with around 1 week in adjusted analyses. Approximately 40% of patients with IMD had sequelae after discharging from hospital. Those patients were 1.5–3 times more likely to stay in hospital longer and visit outpatient clinics during the acute admission and/or in the year following admission [39, 43, 49].

The total cost associated with an outbreak was reported as I$55,778 in Brazil and I$7873 in Colombia [37] (Table 4). As MenB vaccines were not available for the outbreak in Colombia, the cost of managing the outbreak was lower in Colombia than the one in Brazil. It was

Table 1 Characteristics of costing studies included in the systematic review

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of IMD cases	Clinical diagnosis	Serogroup
Clarke and Mallonee [36]	Oklahoma, USA	US$	2002–2004	Not stated	46	All	Not stated	Laboratory confirmed and probable cases of IMD	Not stated
Constenla et al. [37]	Vila Brandina in Brazil and Cartagena de Indias in Columbia	US$	2011 and 2012 (2014 US$)	3 months (Brazil); 18 days (Columbia)	3 in Brazil; 6 in Colombia (outbreak)	All	Brazil: 2 children (aged 3 years) and an adult (aged 36 years); Colombia: 6 children	Laboratory confirmed, probable or clinically suspected IMD	2 confirmed IMD cases in Brazil: C (100%); 4 confirmed IMD cases in Columbia: B (100%)
Davis et al. [38],	USA	US$	2006 (2009 US$)	Not stated	447 (735 [weighted])	≤ 20	Female: 42%; age category: < 1 year (25.99%), 1–4 years (23.67%), 5–10 years (13.74%), 11–18 years (26.94%), 19–20 years (9.66%)	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Davis et al. [39]	USA	US$	1998–2009 (2009 US$)	12 months	173	All	Mean age, year (SD): 33.2 (24.7); female: 52%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Davis et al. [40]	USA	US$	1999–2007 (2009 US$)	12 months	Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS): (n = 349, 1710 [weighted]); Perspective Comparative Database (PCD): (n = 1058 [weighted]); LifeLink Health Plan Database: (n = 268 [weighted])	All	Mean age, year (SD): NIS: 25.10 (55.59), PCD: 31.52 (26.27), Lifelink: 35.18 (26.82); female: 47–49%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Gil-Prieto et al. [41]	Spain	€	1997–2008	Not stated	11,611 discharges	All	Mean age, year (SD): 16 (22); median age, year (interquartile range): 5 (1, 20); female: 48.8%	Diagnosis of IMD defined by ICD-9-CM codes 036	Not stated

Table 1 continued

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of IMD cases	Clinical diagnosis	Serogroup
Hanquet et al. [42]	Belgium	€	2004–10 (2012 Euros)	Up to discharge	698	All	By age group (*n*): < 1 year (117), 1–4 years (169), 5–9 years (77), 10–19 years (165), 20+ years (170)	Diagnosis of IMD defined by ICD-9-CM codes 036	B: *n* = 597
Karve et al. [43]	USA	US$	1997–2009 (2009 US$)	12 months	343	All	Mean age in years (SD): 34.2 (22.6); female: 44.6%	Diagnosis of IMD defined by ICD-9-CM codes in the range of 036.x	Not stated
Letouze et al. [44], 2014	England, UK	£	2012 (2012 £)	Up to discharge	2 (outbreak)	All	2 female primary school pupils aged 10 and 8 years	Laboratory confirmed IMD	B
Montero et al. [45]	Spain	€	1997–2005	Not stated	9479	All	Median age, year (range): 6 years (0–102); female: 49.2%	Diagnosis of IMD defined by ICD-9-CM codes 036	Not stated
O'Brien et al. [46]	California, Florida, Massachusetts and Washington States, USA	US$	1999–2001 (2003 US$)	Up to discharge	1634	All	Mean age, year: 24; median age, year (range): 17 (0–96); female: 48%	Admissions of IMD defined by ICD-9-CM codes 036	Not stated
Pinzon-Redondo et al. [47]	Cartagena de Indias, Colombia	US$	2012 (2011 US$)	3 week following the outbreak	6 (outbreak)	All	Mean age, year (SD): 4.6 (3.5); female: 50%	Laboratory confirmed IMD	B (100%)
Tirani et al. [48]	Lombardia and Piemonte, Italy	€	2007–012 (2013 €)	Not stated	341	All	Female: 51.9%	Discharge diagnosis of IMD defined by ICD-9-CM codes 036	B (59.2%), C (29.6%), others (11.1%)

Table 1 continued

Study	Location	Currency	Study period (year of pricing)	Follow-up period	Sample size	Age group, years	Age and sex of IMD cases	Clinical diagnosis	Serogroup
Wang et al. [49]	Adelaide, SA, Australia	AUS$	2000–11 (2011 AUS$)	5–3659 days	109	< 18	Mean age, year (SD): 3.9 (4.5); female: 54.1%	Laboratory confirmed and probable cases of IMD	B (70.6%), C (9.2%), Y (0.9%), W (1.8%)

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, *IMD* invasive meningococcal disease, *SD* standard deviation

reported in the UK study that the incremental cost of managing a second case of IMD was I$7815 [44].

3.4 Direct Non-medical Costs and Indirect Costs

We have not found any studies reporting direct non-medical costs and indirect costs relevant to IMD. We excluded studies that estimated productivity loss based on assumption or expert opinions without any primary data collection.

3.5 Factors Impacting Healthcare Costs

Studies in USA and Australia suggested sequelae/complications, serogroup B infection, male sex, and previous medical history were significantly associated with higher healthcare costs and resource use compared with their counterparts [5, 38, 39, 43]. Infants aged less than 1 year had the highest healthcare costs and LOS in pediatric patients and young patients aged < 21 years [38, 49]. However, unadjusted mean costs or LOS reported in other studies did not show a similar trend. In contrast, adolescents or adults were reported as having higher costs and longer LOS than other age groups [41, 42, 45, 46, 48].

4 Discussion

This systematic review included 14 studies that reported costs associated with acute infection and/or long-term care of patients with IMD, and descriptively described and compared study results and methodologies. To our knowledge, this is the first study to systematically review and investigate the financial impact of IMD.

The results show a considerable impact of IMD on healthcare resources, which reflects severe outcomes associated with the disease requiring resource-intensive treatments. The costs of acute treatment and readmissions were the most important components of total healthcare costs. The national costs per year were estimated to be around €5 million in Spain [41, 45] and US$50 million in USA [40, 46]. Although total costs of controlling IMD outbreaks are not significant in Brazil and Colombia, the management of outbreaks cost 2.7 times more than the annual gross domestic product per capita in Brazil including vaccination costs and 9.5% of Colombia's annual gross domestic product per capita without using any vaccination [37].

The financial impact of long-term sequelae on the healthcare system has not been well investigated. The included studies consistently reported that the presence of sequelae is an important predictor of high healthcare costs and resource use. Clinical data show that around 10% of patients with IMD had severe long-term sequelae such as

Table 2 Summary of study designs and methods used in included studies

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Clarke and Mallonee [36]	Incidence; bottom up	Healthcare system	State-wide hospital discharge data	Hospital charges	Not stated	No	Not stated	No
Constenla et al. [37]	Incidence; bottom up	Healthcare system	Interviews with structured standardized questionnaires administered to health authorities involved in the outbreak	Personnel, office supplies, gasoline consumption, chemoprophylaxis, and vaccines	Expressed costs in 2014 US dollars using the IMF official exchange rate	No	Not stated	No
Davis et al. [38]	Incidence; bottom up	All payers (private insurance, self-pay, government)	2006 HCUP Kids' Inpatient Database	Total cost per admission	All cost data were converted from charges using facility-specific, cost-to-charge ratios provided by the HCUP and inflated to $US, year 2009 values using the medical component of the US Consumer Price Index.	Demographically matched admissions: $n = 4573$	Healthcare costs: GLM with a log-link function and Gamma distribution; LOS data: zero-truncated negative binomial and Poisson regression models	A binary IMD indicator (IMD admission vs. control), sex (female vs. male), race (white vs. non-white), geographic location, admission source (ED vs. other), urban/rural status of the hospital, teaching/non-teaching status of the hospital, payer type (private insurance vs. non-private) and discharge status (routine vs. dead)
Davis et al. [39]	Incidence; bottom up	Third-party payer	LifeLink database (formerly the PharMetrics Integrated Outcomes Database)	Medical claims and associated costs for various service categories, including inpatient, ED, hospital outpatient services, physician office visits, nursing home services and rehabilitation facilities, pharmacy claims, and associated costs	Adjusted to 2009 US dollars	No	Healthcare costs: GLM with a log-link function and gamma distribution; resource utilization data: negative binomial regression models	Presence of IMD-related sequelae and patient baseline demographic characteristics including age, gender, region, payer type, insurance type and the Charlson Comorbidity Index score

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Davis et al. [40]	Incidence; bottom up	All payers (private insurance, self-pay, government)	HCUP NIS 2005, PCD 2000–2007, and LifeLink (formerly PharMetrics) Health Plan Database 1999–2000	NIS: all-payer inpatient care; PCD: principal and secondary procedures, medications, laboratory tests, and diagnostic and therapeutic services at the individual patient level, as well as the hospital ward (e.g., ICU); LifeLink: actual paid (i.e., reimbursed) amounts for medical services and prescription drugs utilized, and costs of non-facility (i.e., professional and other ancillary) services rendered	All cost data were converted from charges using facility-specific, cost-to-charge ratios provided by the HCUP and inflated to $US, year 2009 values using the medical component of the US Consumer Price Index.	No	Not stated	No
Gil-Prieto et al. [41]	Incidence; bottom up	Healthcare system	National surveillance system for hospital data	The cost to the healthcare system of these hospitalizations was calculated by considering the diagnostic cost group, the total cost, and the number of discharges. Diagnostic cost group was based on the DRG codes for hospitalized patients depending on discharge ICD classification, age, sex, and resource consumption.	Not stated	No	Descriptive analysis only	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Hanquet et al. [42]	Incidence; bottom up	Healthcare payers	Hospital Clinical Records (MZG-RHM: Minimale Ziekenhuisgegevens-Résumé Hospitalier Minimum); Hospital Billing Records database (AZV-SHA: Anoniem Ziekenhuis Verblijf - Séjour Hospitalier Anonyme); database of the National Reference Centre	Healthcare costs of each hospital stay including the extrapolated lump sums for laboratory testing, medical imaging and drugs	Adjusted to 2012 values using the health Consumer Price Index. Before aggregating the costs recorded in each IMD stay, the following adjustments were performed: extrapolation to 100% per diem costs; extrapolating the lump sums for laboratory testing, medical imaging, and drugs.	No	Descriptive analysis only	No
Karve et al. [43]	Incidence; bottom up	Third-party payer	An administrative claims database in USA (Ingenix Impact (formerly the Integrated Healthcare Information Services) database)	Medical claims and associated costs for different service categories including inpatient, ED, outpatient, physician office, nursing home, and rehabilitation services, as well as details on pharmacy utilization and associated costs	Adjusted to 2009 US$	No	Healthcare costs: GLM with a log-link function and gamma distribution; risk of rehospitalization: Cox proportional hazard models; number of hospitalizations or physician office visits: negative binomial regression models	Presence of IMD-related sequelae and patient demographic characteristics including age, sex, region, payer type, insurance type, and co-morbidity burden via the Charlson Comorbidity Index score
Letouze et al. [44]	Incidence; bottom up	Public health management	Published unit costs used to estimate the total cost	Time and cost attributed to staffing, microbiology, pharmacy, and media liaison	Adjusted to 2012 price in pounds	No	Not stated	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Montero et al. [45]	Incidence; bottom up	Healthcare system	National surveillance system for hospital data	The cost to the healthcare system of these hospitalizations: calculated by considering the diagnostic cost group, the total cost and the number of discharges. Diagnostic cost group: based on the DRG codes for hospitalized patient depending on discharge ICD classification, age, sex, and resources consumption	Not stated	No	Descriptive analysis only	No
O'Brien et al. [46]	Incidence; bottom up	Healthcare payers	Claims databases maintained by each individual state, patient discharge databases	Acute hospital costs include all accommodations (e.g., routine, ICU, ancillary services (e.g., pharmacy, laboratory), ED, and observation unit care prior to admission where appropriate, and physician services.	Older values were inflated using rates based on the medical care component of the US Consumer Price Index, supplied by the Federal Bureau of Labour Statistics for the appropriate years. Hospital charges were adjusted to costs using a 0.61 cost-to-charge ratio. State costs [where data from a single state were used (i.e., Florida Medicaid physician fees)] were adjusted to national values using ratios based on published national and state cost data.	No	Not stated	No

Table 2 continued

Study	Method of calculation	Perspective	Data sources	Cost items	Cost adjustments	Controls	Statistical methods	Confounding variable adjustment
Pinzon-Redondo et al. [47]	Incidence; bottom up	National health system	Interviews with experts involved in the outbreak and medical notes review	Direct treatment costs and costs associated with outbreak control including personnel costs, measured in time and estimated as a fraction of the salary of each. An outbreak care team consisted of two pediatricians, two nurses, an epidemiologist, and two public health experts.	All costs are expressed in US$ (2011) as cost per 1000 inhabitants.	No	Not stated	No
Tirani et al. [48]	Incidence; bottom up	Healthcare system	National Invasive Bacterial Diseases Surveillance System; Italian Hospital Discharge Dataset	All hospital-related expenditures (i.e., costs for acute standard care and complications) used the DRG codes reported for each patient record.	Adjusted to 2013 € price level	No	Descriptive analysis only	No
Wang et al. [49]	Incidence; bottom up	Healthcare system	Costing data were provided by the hospital Health Informatics, Performance, Planning and Outcomes Unit. Clinical data were extracted from medical records.	Direct medical costs included costs of medical ward, pathology, imaging, allied health, pharmacy, use of theatre suite, pediatric intensive care unit, prosthesis, medical and surgical supplies, hotel services, direct goods, and services and overheads.	Inflated to 2011 AUS$ using the medical and hospital services component of the Australian Consumer Price Index	No	Healthcare costs: GLM; LOS during the acute admissions: zero-truncated negative binomial regression models; LOS of readmission, the number of outpatient visits and readmission frequencies: negative binomial regression models	Serogroup, age, sex, diagnosis type, previous medical history and sequelae

DRG Diagnosis Related Group, *ED* emergency department, *GLM* generalized linear model, *ICD* International Classification of Diseases, *ICU* intensive care unit, *LOS* length of hospital stay, *NIS* Nationwide Inpatient Sample, *PCD* Perspective Comparative Database

Table 3 Summary of included studies reporting healthcare costs and resource utilization

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization
Clarke and Mallonee [36]	Mean hospital charges per patient: I$46,006 (median: I$22,431, range: I$946–I$328,506)	No	No	Mean LOS per patient in days: 12 (median: 8, range: 1128)	No	NA
Davis et al. [38]	Not stated	Mean costs per admission by age group (95% CI): < 1 year: I$39,620 (I$35,704–I$43,537), 1–4 years: I$13,437 (I$12,875–I$13,999), 11–18 years: I$21,656 (I$20,788–I$22,524), 19–20 years: I$34,163 (I$30,647–I$37,680), all ages I$23,792 (I$22,985–I$24,601)	I$16,378	Not stated	Mean LOS per admission by age group in days (95% CI): < 1 year: 9.0 (7.7–10.3), 1–4 years: 5.51 (5.07–5.95), 5–10 years: 5.55 (4.64–6.46), 11–18 years: 6.20 (5.84–6.56), 19–20 years: 8.99 (7.53–10.45), all ages: 6.4 (6.0–6.8)	LOS per patient in days: 4.3
Davis et al. [39]	Mean healthcare costs during 12 mo per patient (SD): I$60,540 (I$132,314) including inpatient costs of I$50,796 (I$119,472) for all patients, I$83,923 (I$145,990) including inpatient costs of I$70,660 (I$133,151) for patients with complicated IMD, I$44,263 (I$119,961) including inpatient costs of 36,969 (I$107,469) for patients with uncomplicated IMD	Mean healthcare costs during 12 mo per patient (95% CI): I$78,364 (I$67,592–I$89,134) including inpatient cost of I$67,633 for patients with complicated IMD, I$45,521 (I$41,162–I$49,880) including inpatient cost of I$38,342 for patients with uncomplicated IMD	No	Mean LOS during 12 mo per patient in days (SD): 17.8 (26.8) for all patients, 26.7 (31.7) for patients with complicated IMD, 11.5 (20.7) for patients with uncomplicated IMD; mean number of rehospitalization per patient (SD): 0.64 (1.30) for all patients, 1.1 (1.7) for patients with complicated IMD, 0.3 (0.9) for patients with uncomplicated IMD	Inpatient admissions during 12 mo: IRR = 1.5 (95% CI 1.2–1.9) for patients with complicated IMD vs. patients with uncomplicated IMD; hospital outpatient visits: IRR = 3.2 (95% CI 1.7–5.8) for patients with complicated IMD vs. patients with uncomplicated IMD; home health and durable medical equipment services: IRR = 2.7 (95% CI 1.0–6.9) for patients with complicated IMD vs. patients with uncomplicated IMD	No
Davis et al. [40]	Mean acute admission costs per patient: I$48,146; mean follow-up care costs following discharge from initial admission: I$23,565 including costs attributed to repeat hospitalizations of I$15,908; mean 1-year cost: I$71,711	No	No	Mean LOS during acute admission per patient in days: 9; mean ICU stay in days: 1.7	No	No
Gil-Prieto et al. [41]	Mean costs per admission: I$7843	No	No	Mean LOS per admission by age group in days (SD): < 1 year: 10 (9), < 2 years: 10 (9), 0–4 years: 10 (10), 5–9 years: 9 (8), 10–14 years: 11 (11), 15–19 years: 12 (11), 20–24 years: 12 (14), 25–29 years: 13 (11), 30–49 years: 15 (21), 50–54 years: 17 (18), 55–59 years: 16 (17), 60–64 years: 19 (25), 65–69 years: 16 (15), 70–74 years: 15 (14), 75–79 years: 17 (19), 80–84 years: 14 (12), ≥ 85 years: 12 (8), all ages: 11 (12)	No	No

Table 3 continued

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization
Hanquet et al. [42]	Mean acute admission costs per patient (SD): serogroup B only by age group: < 1 year: I$8998 (I$10,193), 1–4 years: I$7,655 (I$6061), 5–9 years: I$6774 (I$2553), 10–19 years: I$9752 (I$8,430), 20+ years: I$12,278 (I$9,874), all ages: I$9182 (I$8211); any serogroup by age group: < 1 year: I$8844 (I$9665), 1–4 years: I$7674 (I$6017), 5–9 years: I$7326 (I$4305), 10–19 years: I$9733 (I$8238), 20+ years: I$12,926 (I$13,643), all ages: I$9597 (I$9574)	No	No	No	No	No
Karve et al. [43]	Mean healthcare costs during 12 mo per patient (SD): I$59,779 (I$118,314) including inpatient costs of I$45,162 (I$104,901) for all patients, I$108,406 (I$187,826) including inpatient costs of I$81,383 (I$168,945) for patients with complicated IMD, I$34,605 (I$34,972) including inpatient costs of I$26,410 (I$31,238) for patients with uncomplicated IMD	Mean healthcare costs during 12 mo per patient (95% CI): I$105,235 (I$96,360–I$114,113) including inpatient costs of I$77,868 (I$71,741–I$83,996) for complicated patients, I$35,229 (I$33,502–I$36,957) including inpatient costs of I$26,995 (I$25,667–I$28,322) for uncomplicated patients	No	Mean LOS during 12 mo in days (SD): 14.0 (27.6) for all patients, 25.6 (42.3) for patients with complicated IMD, 8.1 (11.3) for patients with uncomplicated IMD; mean number of rehospitalization (SD): 0.5 (1.3) for all patients, 1.0 (2.0) for patients with complicated IMD, 0.2 (0.6) for patients with uncomplicated IMD; mean number of hospital outpatient visits (SD): 6.4 (11.9) for all patients, 12.7 (17.9) for patients with complicated IMD, 3.1 (4.5) for patients with uncomplicated IMD	Inpatient admissions during follow-up: IRR = 1.5 (95% CI 1.3–1.9) for complicated patients vs. uncomplicated patients; outpatient visit: IRR = 3.1 (95% CI 2.4; IRR 4.0) for complicated patients vs. uncomplicated patients; rehospitalization after initial IMD admission: hazard ratio = 1.7 (95% CI 1.0; IRR 2.7) for complicated patients vs. uncomplicated patients	
Montero et al. [45]	Mean cost per admission: I$7791	No	No	Mean LOS per admission by age group in days (95% CI): 0–4 years: 9.81 (9.53–10.09), 5–9 years: 9.10 (8.66–9.53), 10–14 years: 10.54 (9.69–11.39), 15–19 years: 11.32 (10.65–11.98), 20–24 years: 12.03 (10.98–13.08), 25–29 years: 12.53 (11.14–13.91), ≥ 30 years 15.56 (14.71–16.40), all ages: 11.10 (10.86–11.33)	No	No
O'Brien et al. [46]	Mean acute admission cost per patient by age group: < 1 year: I$21,043, 1–10 years: I$25,418, 11–17 years: I$35,339, 18–22 years: I$32,908, 22–49 years: I$33,958, ≥ 50 years: I$26,816, all ages: I$29,189 (median: I$14,591)	No	No	Mean LOS per survivor in days: 8.8 (median: 6.5)	No	No

Table 3 continued

References	Unadjusted healthcare costs	Adjusted healthcare costs	Incremental costs	Unadjusted healthcare utilization results	Adjusted healthcare utilization results	Incremental healthcare utilization
Tirani et al. [48]	Mean admission costs per patient (range): pediatric (≤ 18 years): I$9067 (I$3334–I$50,671), adult (> 18 years): I$11,001 (I$3600–I$60,005)	No	No	Mean LOS per patient in days: 11.40 for subjects ≤ 18 years (pediatric) and 21.64 for those > 18 years (adult); by age group: < 1 year: 10.92, 1–4 years: 12.29, 5–9 years: 10.88, 10–14 years: 10.15, 15–19 years: 12.76, 20–24 years: 13.90, 25–44 years: 28.34, 45–64 years: 22.08, 60+ years: 22.25	No	No
Wang, et al. [49]	Mean acute admission costs per patient (95% CI): I$14,855 (I$8618–I$25,064) for all patients, I$29,140 (I$13,573–I$54,868) for patients with sequelae, I$11,529 (I$4,558–I$6075) for patients without sequelae, I$17,644 (I$9288–I$32,827) for MenB patients, I$8144 (I$5207–I$13,571) for non-MenB patients, I$22,451 (I$9451–I$49,725) for patients < 1 year, I$11,698 (I$6783–I$22,350) for patients ≥ 1 year; mean readmission costs for patients with sequelae (95% CI): I$7905 (I$1041–I$17,439)	Mean acute admission costs per patient (95% CI): I$8571 (I$7317–I$9824) for all patients, I$24,591 (I$22,212–I$26,968) for patients with sequelae, I$5743 (I$5352–I$6135) for patients without sequelae, I$16,550 (I$13,647–I$19,453) for MenB patients, I$7191 (I$6150–I$8232) for non-MenB patients, I$16,511 (I$13,360–I$19,662) for patients < 1 year, I$12,864 (I$10,544–I$15,183) for patients ≥ 1 year; mean readmission costs for patients with sequelae (95% CI): I$935 (I$248–I$1621)	No	Mean LOS during acute admissions in days (95% CI): 9.6 (7.1–13.6) for all patients, 16.5 (10.0–27.3) for patients with sequelae, 5.3 (4.7–6.0) for patients without sequelae, 11.3 (7.6–17.3) for MenB patients, 5.5 (4.6–7.0) for non-MenB patients, 12.5 (7.8–21.6) for patients < 1 year, 8.4 (5.9–13.6) for patients ≥ 1 year; mean readmission LOS in days (95% CI): 4.8 (0.7–10.6) for patients with sequelae	Mean LOS during acute admissions in days (95% CI): 7.2 (6.1–8.4) for all patients, 14.3 (13.3–15.3) for patients with sequelae, 5.2 (4.9–5.6) for patients without sequelae, 10.3 (9.1–11.6) for MenB patients, 5.3 (4.7–6.0) for non-MenB patients, 10.1 (8.8–11.4) for patients < 1 year, 8.5 (7.4–9.6) for patients ≥ 1 year; mean readmission LOS in days (95% CI): 1.1 (0.2–21) for patients with sequelae	No

CI confidence interval, *IMD* invasive meningococcal disease, *IRR* incidence rate ratio, *LOS* length of hospital stay, *NA, SD* standard deviation

Table 4 Summary of included studies reporting healthcare costs and resource utilization during outbreaks

References	Cost items and type of resource	Unadjusted costs and resource utilization	Incremental costs
Constenla et al. [37]	Personnel, office supplies, gasoline consumption, chemoprophylaxis, and vaccines	Colombia: total cost of investigation and outbreak management: I$1239 (I$207 per notified case); total cost of disease surveillance: I$6634 Brazil: total cost of investigation and outbreak management: I$46,728 (I$15,576 per notified case), total cost of disease surveillance: I$9050	No
Letouze et al. [44]	Time and cost attributed to staffing, microbiology, pharmacy, and media liaison	Total cost of managing an outbreak (two cases): I$8286, total cost of managing a single case: I$471	I$7815
Pinzon-Redondo et al. [47]	Direct treatment costs and costs associated with outbreak control including personnel costs, measured in time and estimated as a fraction of the salary of each. An outbreak care team consisted of two pediatricians, two nurses, an epidemiologist, and two public health experts.	Mean cost of hospital care per patient: I$1629 (median: I$1332); total cost of the disease response phase: I$1216; total cost of disease surveillance: I$6511	No

amputation, skin scarring, or neurological disabilities [1, 2, 5]. However, most patients were only followed up until discharge, and costs for other healthcare services such as rehabilitation associated with long-term care were not included. Studies in USA followed patients up to 12 months post-discharge [39, 43] and one study in Australia assessed readmission costs in one tertiary pediatric hospital [49]. Including costs relevant to care and clinical management of long-term sequelae may lead to substantially higher cost estimates. A few case studies show that the discounted lifetime cost associated with severe long-term sequelae could be more than €1 million. However, those severe IMD cases were developed on the basis of expert opinions and interviews with patients and their families [50–52]. Future studies are warranted to investigate the longer term financial burden imposed on the healthcare system, patients, their families, and society as well as the negative effect on economically meaningful health outcomes (e.g., quality of life) [53, 54]. The cost and quality of life are key inputs into health economic evaluation, and therefore reliable data on the costs of long-term care would be valuable in reducing parameter uncertainty.

Undertaking studies to follow patients with IMD over a long period of time (e.g., lifetime) could be time and resource consuming. It might be problematic to link different administrative, costing, and clinical databases, as researchers would need to follow ethics, privacy, and legal guidelines and fulfill local and national requirements. Because the incidence rate of IMD peaks in infants [55], those infant survivors with neurological sequelae and motor deficits would need multiple hospital readmissions, special education, and long-term carers. The time frame of follow-up is a critical point to consider. For example, following adult patients until their conditions stabilize may only take 2 years. It may take at least 3–5 years to confirm diagnoses of permanent neurological and psychological sequelae in infant survivors. Given the previous literature indicating that around 20–40% of IMD survivors had multiple sequelae following IMD [1, 56], determining the long-term effect of each single sequela separately could be very difficult. The cost associated with individual sequela has been used to develop decision analytical models to assess the cost effectiveness of meningococcal vaccines. Those parameters were determined mainly on the basis of data collected for similar medical conditions, assumptions, or expert opinions [42, 48, 57, 58].

The impact of the disease on individuals and the community has been widely discussed and considered substantial [19, 20], but we have not found any studies reporting data associated with direct non-healthcare costs and indirect costs. The financial burden of the disease estimated in our review was relatively conservative, as third-party payers were the only perspective taken by the included studies. The measurement of reduced employment, absenteeism, presenteeism, and productivity loss associated with informal carers is controversial [59]. In a small number of cost-effectiveness studies taking the societal perspective, the productivity costs were based on assumptions or average national employment data [57, 58, 60].

Our review found that around one third of included studies reported costing results by serogroup [37, 42, 44, 47, 49]. One study compared serogroup B with non-B and reported serogroup B disease was likely to result in the highest costs to the healthcare system in pediatric patients [49]. Clinical literature indicated serogroup C disease was associated with high rates of morbidity and mortality [1, 61]. The serogroup may be an important

factor in predicting the disease severity and hence healthcare expenditures. Cost-of-illness analyses should reflect the epidemiology of the disease and variations in serogroup distribution in relation to time period and geographical region. Serogroup comparison may be necessary to consider in COI analyses to support cost-effectiveness evaluations assessing vaccines against certain serogroups. Because of the limited number of COI studies examining the effect of serogroups on healthcare costs, some cost-effectiveness studies used the average acute admission cost for all IMD cases derived from International Classification of Diseases codes [48, 62]. Several studies estimated the average acute hospitalization cost based on Diagnosis Related Group costs associated with meningococcal diagnosis [57, 58].

Although the new MenB vaccines are protein based, the preliminary results obtained from studies evaluating the impact of meningococcal vaccines on disease carriage prevalence show that MenB vaccines could potentially offer a certain level of protection against non-B serogroup disease [63]. All MenB vaccines are licensed to provide protection against serogroup B disease only. Serogroup-specific COI analyses may still be warranted to provide useful information on disease burden for cost-effectiveness evaluations. Pentavalent vaccines that protect against five serogroups (A, B, C, W, and Y) causing the majority of IMD are currently in phase III clinical trials. It may be less important to compare and evaluate healthcare resource use by serogroup in a decade.

Invasive meningococcal disease has become uncommon especially in industrialized countries, which may be owing to vaccine pressure, a reduction in smoking, or natural fluctuations of disease incidence [55]. However, outbreaks of IMD continue to occur in schools and universities [64, 65]. Surveillance networks have closely monitored capsule switching and capsule replacement after implementing meningococcal vaccination programs. The impact of the new protein-based MenB vaccines on clearing carriage and interrupting transmission in adolescents remains unclear. It is too early to envisage eradication of the meningococcus bacteria at the current stage, when most developing countries have not implemented meningococcal vaccine programs because of the high costs of vaccines [66]. Although inclusion of the MenB vaccine on the government-funded National Immunisation Program was rejected by the Pharmaceutical Benefits Advisory Committee in Australia, the Australian Technical Advisory Group on Immunisation provided clinical advice to the Pharmaceutical Benefits Advisory Committee and recommended routine MenB vaccination of infants, young children, and adolescents owing to their higher risk of MenB infection [11, 67]. The COI analyses would still be required to inform a cost-effectiveness review of a new submission or resubmission to national decision-making bodies for publicly funding new meningococcal vaccines. However, we acknowledge that the evaluation of the true costs of IMD may be more challenging in the future because of a reduced number of patients infected with IMD.

The incremental cost-effectiveness ratios derived from the estimate of costs and quality-adjusted life-years are one of the key inputs to inform public funding decisions in countries such as the UK and Australia. An evaluation of IMD vaccines by national funding bodies in Australia and the UK found that the results of economic evaluations of meningococcal prevention strategies were, among others, highly sensitive to herd immunity and vaccine effectiveness [12, 15]. After considering new evidence in 2014, the JCVI recommended the MenB vaccine for inclusion on the UK national immunization program with a reduced dose schedule at a very low price of £7 per dose based on the revised analysis [16]. Including litigation costs associated with the disease, updating cost data relevant to long-term care, and using a quality-of-life adjustment factor affected the outcome of a cost-effectiveness analysis in the UK [15]. With very limited COI analyses conducted for this severe but uncommon disease, there may be a risk of underestimating the true disease burden. The results of model-based evaluations are subject to a significant level of parameter uncertainty as emphasized by the Global Meningococcal Initiative [68]. Because of considerable uncertainty around the duration of protection against IMD and potential for reduction in the carriage in adolescents, the JCVI rejected the inclusion of the routine MenB vaccine schedule in adolescents. If the true value of COI is ultimately shown to be high enough, for example, considering all important direct and societal costs, it may be argued that this could potentially offset the significance of indirect protective effects/herd immunity that play an important role in determining the cost effectiveness of new meningococcal vaccine programs.

Therefore, comprehensive COI analyses could provide important inputs into economic evaluations of meningococcal vaccines to better inform public funding decisions. It is worth noting that individuals, charity organizations, and clinicians strongly criticized the JCVI's initial rejection and called for re-evaluation of the vaccine program. Subsequently, the JCVI reviewed and revised the analysis that included more favorable assumptions, optimized parameters, and additional costs associated with the disease, thereby amending its interim position [69]. Economic evidence is only one of several inputs into decision making. Guidelines developed by decision-making bodies in countries such as Australia and Canada recommend considering less-readily quantifiable factors for health technology funding decisions [70, 71]. In Australia, for example, national funding bodies consider factors such as

severity and rapid onset of the condition under study, the age at which a person with the condition might die, and rarity of the condition. Such societal values are all relevant to IMD and hence should be considered in evaluating IMD-related vaccines. However, as reported by Drew et al., there is a lack of transparency and consistency in defining and integrating these values into decision making [72].

The quality and methodologies varied significantly between studies. Although we converted costs from original studies to international dollars, extremely high heterogeneity including differences in the treated population, study design, cost items, or data analysis hinders direct comparison between studies, which may also explain the conflicting results of inpatient costs and healthcare resource use in infants. The included studies used insurance claims, hospital charges, or payments to estimate costs that may not represent the same 'market value' between studies. Only four out of 14 studies reported adjusted mean values using a regression model to adjust for confounding factors including sociodemographic characteristics, disease outcomes, comorbidities, and/or medical history. Differences between unadjusted and adjusted mean values were apparent within the same study, reflecting the importance of consideration of potential confounders in any analyses.

It is of concern that overlooking the nature of highly skewed costing data and not using any appropriate statistical models to deal with skewness and adjusting for potential confounders could lead to biased results [18, 26, 73]. Among those studies presenting only unadjusted results, four studies reported average costs and/or LOS without any variability measures. Incremental costs are commonly recommended for health economic analyses and have been frequently reported in the COI studies of other diseases [26, 28, 74]. The incremental costs were only reported in one included study through a comparison of patients with IMD with matched controls.

We understand various methodologies are used to generate estimates in the COI studies to serve different purposes [75]. However, this variation in study conduct may also reflect a lack of guidelines to standardize COI study designs and methodologies [76]. A review of COI studies highlighted the need for standardized methods of cost calculation, mathematical modeling, choice of cost components, disease classification, and selection of study perspective [77]. The findings of COI studies are often used to support funding decisions and attract public attention. Developing and implementing best-practice recommendations will improve the comparability and generalizability of the costing studies.

As some studies enrolled patients with meningitis caused by a range of bacteria, including *Haemophilus influenzae* type B, *Neisseria meningitides*, and *Streptococcus pneumoniae*, we were unable to separate the costs for patients with meningococcal meningitis from those with other bacterial meningitis. We excluded studies describing the financial burden of meningitis during epidemics of serogroup A meningococcal disease in the meningitis belt of sub-Saharan Africa because those studies did not report costs associated with meningococcal meningitis specifically. Because the authors' first language is English and not all languages were included, there may be important studies not included in this review, resulting in regional or English-language bias.

5 Conclusions

Despite the variability in estimates of medical costs and hospital resource use, all included studies concluded IMD resulted in substantial costs to healthcare systems or third-party payers. The public concerns and fears caused by IMD have been frequently reported. However, few have implemented appropriate research methods, for example, using micro-costing methodology and collecting primary data prospectively from the societal perspective [22], to investigate the true costs of the disease. This systematic review provides important information for the selection of an appropriate unit cost for future cost-effectiveness studies, identifying the financial burden of the disease in prioritizing healthcare policies, and estimating potential cost savings accrued from the introduction of new vaccines, and also reinforces the need to standardize methodology and improve the quality of the COI studies.

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Author contributions BW, HM, LG, and HA conceived and designed the study. BW conducted the database searches, extracted, analyzed, and interpreted the data, performed a quality assessment, and produced the draft of the manuscript. RS extracted data and performed a quality assessment. HM, RS, LG, and HA contributed to, reviewed, and edited the manuscript. HM acts as the overall guarantor.

Data Availability Statement The full dataset including data extracted from the full-text review and quality assessment results that support the findings of this study are available from the corresponding author upon request. The authors declare that all other data supporting the findings of this study are available within the article and its supplementary information files.

Compliance with Ethical Standards

Conflict of interest Helen Marshall is an independent investigator on clinical trials of investigational vaccines manufactured by pharmaceutical companies including GlaxoSmithKline, Novavax, and Pfizer. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, Pfizer, and Novartis Vaccines. Bing Wang, Renee Santoreneos, Hossein Afzali, and Lynne Giles

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References

1. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J. 2013;32(1):e20–5.
2. Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. 2012;11(9):774–83.
3. Edge C, Waight P, Ribeiro S, Borrow R, Ramsay M, Ladhani SN. Clinical diagnoses and outcomes of 4,619 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: linkage analysis of multiple national databases. J Infect. 2016;73(5):427–36.
4. Nadel S. Prospects for eradication of meningococcal disease. Arch Dis Child. 2012;97(11):993–8.
5. Wang B, Clarke M, Thomas N, Howell S, Afzali HH, Marshall H. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. Pediatr Infect Dis J. 2014;33(3):316–8.
6. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009;24(27 Suppl. 2):B51–63.
7. Department of Health Australian Government. Invasive meningococcal disease: national surveillance report, with a focus on MenW, December 2016 [updated 13 Oct 2017]. https://acpc.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/IMD-Surveillance-report20161212.pdf. Accessed 31 May 2018.
8. Lahra MM, Enriquez RP. Australian meningococcal surveillance programme annual report, 2015. Commun Dis Intell Q Rep. 2016;40(4):E503–11.
9. European Centre for Disease Prevention and Control. Annual epidemiological report 2016: invasive meningococcal disease (2014 data). Stockholm: ECDC; 2016. https://ecdc.europa.eu/en/publications-data/invasive-meningococcal-disease-annual-epidemiological-report-2016-2014-data. Accessed 25 Jul 2017.
10. National Center for Immunization and Respiratory Diseases. Enhanced meningococcal disease surveillance report, 2015 [updated 9 June 2017]. https://www.cdc.gov/meningococcal/downloads/NCIRD-EMS-Report.pdf. Accessed 25 Jul 2017.
11. Pharmaceutical Benefits Advisory Committee. Multicomponent meningococcal group B vaccine, 0.5 mL, injection, prefilled syringe, Bexsero®: July 2015. Pharmaceutical Benefits Scheme; 2014. http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2015-07/mulit-component-meningococcal-group-b-vaccine-psd-july-2015. Accessed 25 Jul 2017.
12. Pharmaceutical Benefits Advisory Committee. Multicomponent meningococcal group B vaccine, 0.5 mL, injection, prefilled syringe, Bexsero®: July 2014. Pharmaceutical Benefits Scheme; 2014. http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-07/meningococcal-vaccine-psd-07-2014. Accessed 25 Jul 2017.
13. Pharmaceutical Benefits Advisory Committee. Multicomponent meningococcal group B vaccine, 0.5 mL, injection, prefilled syringe, Bexsero®: November 2013. Pharmaceutical Benefits Scheme; 2013. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/meningococcal-vaccine. Accessed 25 Jul 2017.
14. Joint Committee on Vaccination and Immunisation (JCVI). JCVI interim position statement on use of Bexsero® meningococcal B vaccine in the UK 2013 [updated July 2013]. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224896/JCVI_interim_statement_on_meningococcal_B_vaccination_for_web.pdf. Accessed 25 Jul 2017.
15. Joint Committee on Vaccination and Immunisation (JCVI). JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK 2014 [updated 21 March 2014]. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/252859/JCVI_MenB_Update.pdf. Accessed 5 Sep 2017.
16. Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. BMJ. 2014;349:g5725.
17. Tu HA, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, et al. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. Vaccine. 2014;32(42):5436–46.
18. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmacoeconomics. 2011;29(8):653–71.
19. Anonychuk A, Woo G, Vyse A, Demarteau N, Tricco AC. The cost and public health burden of invasive meningococcal disease outbreaks: a systematic review. Pharmacoeconomics. 2013;31(7):563–76.
20. Martinon-Torres F. Deciphering the burden of meningococcal disease: conventional and under-recognized elements. J Adolesc Health. 2016;59(2 Suppl.):S12–20.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;21(339):b2700.
22. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.
23. Motheral B, Brooks J, Clark MA, Crown WH, Davey P, Hutchins D, et al. A checklist for retrospective database studies: report of the ISPOR Task Force on Retrospective Databases. Value Health. 2003;6(2):90–7.
24. Kleine-Budde K, Touil E, Moock J, Bramesfeld A, Kawohl W, Rossler W. Cost of illness for bipolar disorder: a systematic review of the economic burden. Bipolar Disord. 2014;16(4):337–53.
25. Ernstsson O, Gyllensten H, Alexanderson K, Tinghog P, Friberg E, Norlund A. Cost of illness of multiple sclerosis: a systematic review. PLoS One. 2016;11(7):e0159129.
26. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. Value Health. 2016;19(5):602–13.
27. Jarbrink K, Ni G, Sonnergren H, Schmidtchen A, Pang C, Bajpai R, et al. The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Syst Rev. 2017;6(1):15.
28. Budhia S, Mikyas Y, Tang M, Badamgarav E. Osteoporotic fractures: a systematic review of U.S. healthcare costs and resource utilization. Pharmacoeconomics. 2012;30(2):147–70.
29. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. Pharmacoeconomics. 2015;33(8):811–31.
30. Wodchis WP, Bhatia RS, Leblanc K, Meshkat N, Morra D. A review of the cost of atrial fibrillation. Value Health. 2012;15(2):240–8.
31. Bahia L, Toscano CM, Takemoto ML, Araujo DV. Systematic review of pneumococcal disease costs and productivity loss

studies in Latin America and the Caribbean. Vaccine. 2013;2(31 Suppl. 3):C33–44.
32. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evid Policy. 2010;6(1):51–9.
33. OANDA. Historical exchange rates 2018 [cited 23 April 2018]. https://www.oanda.com/fx-for-business/historical-rates. Accessed 31 May 2018.
34. Kontopantelis E, Reeves D. metaan: random-effects meta-analysis. Stata J. 2010;10(3):395.
35. StataCorp. Stata statistical software: release 14. College Station: StataCorp LP; 2015.
36. Clarke C, Mallonee S. State-based surveillance to determine trends in meningococcal disease. Public Health Rep. 2009;124(2):280–7.
37. Constenla D, Carvalho A, Alvis Guzman N. Economic impact of meningococcal outbreaks in Brazil and Colombia. Open Forum Infect Dis. 2015;2(4):ofv167.
38. Davis KL, Bell TJ, Miller JM, Misurski DA, Bapat B. Hospital costs, length of stay and mortality associated with childhood, adolescent and young adult meningococcal disease in the US. Appl Health Econ Health Policy. 2011;9(3):197–207.
39. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. Hum Vaccin. 2011;7(4):458–65.
40. Davis KL, Misurski D, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the US. Hum Vaccin. 2011;7(1):96–101.
41. Gil-Prieto R, Garcia-Garcia L, Alvaro-Meca A, Gonzalez-Escalada A, Viguera Ester P, Gil De Miguel A. The burden of hospitalizations for meningococcal infection in Spain (1997–2008). Vaccine. 2011;29(34):5765–70.
42. Hanquet GC, Agnew E, Trotter CL, Robays J, Dubois, Devriese S, et al. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study. Health technology assessment (HTA). 2014; KCE reports 231.
43. Karve S, Misurski D, Miller J, Davis KL. Costs of sequelae associated with invasive meningococcal disease: findings from a US managed care population. Health Outcomes Res Med. 2011;2(4):e215–26.
44. Letouze D, Yao G, Clarke SC. The costs associated with the public health management of a cluster of meningococcal infection in England. Vaccine. 2014;32(43):5549–51.
45. Montero JM, Prieto RG, Alejandre CG, Meca LA, Portugal P, de Miguel AG. Hospital admissions for meningococcal infection in Spain (1997–2005). J Infect. 2009;58(1):15–20.
46. O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: hospital case characteristics and costs by age. Value Health. 2006;9(4):236–43.
47. Pinzon-Redondo H, Coronell-Rodriguez W, Diaz-Martinez I, Guzman-Corena A, Constenla D, Alvis-Guzman N. Estimating costs associated with a community outbreak of meningococcal disease in a colombian Caribbean city. J Health Popul Nutr. 2014;32(3):539–48.
48. Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new MenB vaccine (Bexsero) into the Italian routine infant immunisation programme. PLoS One. 2015;10(4):e0123383.
49. Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine. 2014;32(37):4791–8.
50. Benard S, Wright C, Voisine J, Olivier CW, Gaudelus J. Lifetime cost of meningococcal disease in France: scenarios of severe meningitis and septicemia with purpura fulminans. J Infect Public Health. 2016;9(3):339–47.
51. Darba J, Kaskens L, Hark M, Wright C. Costs of surviving meningococcal disease in Spain: evaluation for two cases of severe meningitis and septicaemia. Vaccine. 2014;32(39):5006–12.
52. Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease: scenarios of severe meningitis and septicemia. Paediatr Drugs. 2013;15(1):49–58.
53. Kennedy ITR, van Hoek AJ, Ribeiro S, Christensen H, Edmunds WJ, Ramsay ME, et al. Short-term changes in the health state of children with group B meningococcal disease: a prospective, national cohort study. PLoS One. 2017;12(5):e0177082.
54. Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther. 2013;11(6):597–604.
55. Pelton SI. The global evolution of meningococcal epidemiology following the introduction of meningococcal vaccines. J Adolesc Health. 2016;59(2 Suppl.):S3–11.
56. Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis. 2015;60(8):e27–35.
57. Christensen H, Irving T, Koch J, Trotter CL, Ultsch B, Weidemann F, et al. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero® to reduce meningococcal group B disease in Germany. Vaccine. 2016;34(29):3412–9.
58. Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero®) against meningococcal B disease: a cost-effectiveness analysis. Hum Vaccin Immunother. 2016;12(8):2148–61.
59. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015. p. 245–50.
60. Hepkema H, Pouwels KB, van der Ende A, Westra TA, Postma MJ. Meningococcal serogroup A, C, W(1)(3)(5) and Y conjugated vaccine: a cost-effectiveness analysis in the Netherlands. PLoS One. 2013;8(5):e65036.
61. Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990–1994. Rev Infect Dis. 1998;26(5):1159–64.
62. Lecocq H, Parent du Chatelet I, Taha MK, Levy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine. 2016;34(19):2240–50.
63. Balmer P, Burman C, Serra L, York LJ. Impact of meningococcal vaccination on carriage and disease transmission: a review of the literature. Hum Vaccin Immunother. 2018. https://doi.org/10.1080/21645515.2018.1454570 **(Epub ahead of print)**.
64. Breakwell L, Whaley M, Khan UI, Bandy U, Alexander-Scott N, Dupont L, et al. Meningococcal carriage among a university student population: United States, 2015. Vaccine. 2018;36(1):29–35.
65. McNamara LA, Thomas JD, MacNeil J, Chang HY, Day M, Fisher E, et al. Meningococcal carriage following a vaccination campaign with MenB-4C and MenB-FHbp in response to a university serogroup B meningococcal disease outbreak: Oregon, 2015–2016. J Infect Dis. 2017;216(9):1130–40.
66. Shaker R, Fayad D, Dbaibo G. Challenges and opportunities for meningococcal vaccination in the developing world. Hum Vaccin Immunother. 2018. https://doi.org/10.1080/21645515.2018.1434463 **(Epub ahead of print)**.
67. Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. 10th ed. Canberra: Australian Government Department of Health; 2015 **(2015 update)**.
68. Borrow R, Alarcon P, Carlos J, Caugant DA, Christensen H, Debbag R, et al. The Global Meningococcal Initiative: global

epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines. 2017;16(4):313–28.
69. Timmis JK, Black S, Rappuoli R. Improving accountability in vaccine decision-making. Expert Rev Vaccines. 2017;16(11):1057–66.
70. Committee Pharmaceutical Benefits Advisory. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0). Canberra: Australian Government Department of Health and Ageing; 2016.
71. Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine. 2005;23(19):2470–6.
72. Carter D, Vogan A, Haji Ali Afzali H. Governments need better guidance to maximise value for money: the case of Australia's Pharmaceutical Benefits Advisory Committee. Appl Health Econ Health Policy. 2016;14(4):401–7.
73. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ. 2011;20(8):897–916.
74. Desmedt M, Vertriest S, Hellings J, Bergs J, Dessers E, Vankrunkelsven P, et al. Economic impact of integrated care models for patients with chronic diseases: a systematic review. Value Health. 2016;19(6):892–902.
75. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20(4):327–37.
76. Jacobs P, Ohinmaa A, Brady B. Providing systematic guidance in pharmacoeconomic guidelines for analysing costs. Pharmacoeconomics. 2005;23(2):143–53.
77. Onukwugha E, McRae J, Kravetz A, Varga S, Khairnar R, Mullins CD. Cost-of-illness studies: an updated review of current methods. Pharmacoeconomics. 2016;34(1):43–58.

3.1.4 MENINGOCOCCAL VACCINES

IMD vaccines are available to protect against five major serogroups: A, B, C, W, Y. In this section, the disease burden, vaccine development, and vaccination strategies were reviewed and discussed in the published journal article entitled “Control of invasive meningococcal disease: Is it achievable?”.

3.1.4.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Control of invasive meningococcal disease: is it achievable?
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Marshall H, Wang B, Wesselingh S, Snape M, Pollard AJ. Control of invasive meningococcal disease: is it achievable? International Journal of Evidence-Based Healthcare 2016; 14(1): 3-14.

Principal Author

Name of Principal Author	Helen Marshall		
Contribution to the Paper	HM prepared the first draft of the manuscript and edited the manuscript.		
Overall percentage (%)	65%		
Signature		Date	04 OCT 2018

Name of Co-Author (Candidate)	Bing Wang		
Contribution to the Paper	BW assisted HM in preparing the first draft of the manuscript, and contributed to, reviewed and edited the manuscript. (25%)		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the second co-author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Steve Wesselingh		
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Statement of Authorship

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Contribution to the Paper	HM prepared the first draft of the manuscript and edited the manuscript		
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Name of Co-Author (Candidate)	Bing Wang		
Contribution to the Paper	BW assisted HM in preparing the first draft of the manuscript, and contributed to, reviewed and edited the manuscript. (25%)		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the second co-author of this paper.		
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3.1.4.2 PUBLICATION

DISCUSSION PAPER

Control of invasive meningococcal disease: is it achievable?

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ABSTRACT

Neisseria meningitidis still leads to deaths and severe disability in children, adolescents and adults. Six different capsular groups of *N. meningitidis* cause invasive meningococcal disease in the form of meningitis and septicaemia in humans. Although conjugate meningococcal vaccines have been developed to provide protection against four of the capsular groups causing most diseases in humans, vaccines against capsular group B, which causes 85% of cases in Australia and the United Kingdom, have only recently been developed. A capsular group B meningococcal vaccine – 4CMenB (Bexsero) – has recently been licensed in the European Union, Canada and Australia. In Australia, a submission for inclusion of 4CMenB in the funded national immunization programme has recently been rejected. The vaccine will now be introduced into the national immunization programme in the United Kingdom following negotiation of a cost-effective price. With the current low incidence of invasive meningococcal disease in many regions, cost-effectiveness of a new capsular group B meningococcal vaccine is borderline in both the United Kingdom and Australia. Cost-effectiveness of an infant programme is determined largely by the direct protection of those vaccinated and is driven by the higher rate of disease in this age group. However, for an adolescent programme to be cost-effective, it must provide both long-term protection against both disease and carriage. The potential of vaccination to reduce the rate of severe invasive disease is a real possibility. A dual approach using both an infant and adolescent immunization programme to provide direct protection to those age groups at highest risk of meningococcal disease and to optimize the potential herd immunity effects is likely to be the most effective means of reducing invasive meningococcal disease. This commentary aims to describe the known disease burden and consequences of meningococcal disease, and the development and potential effectiveness of new capsular group B meningococcal vaccines.

Key words: carriage, herd immunity, immunization policy, invasive meningococcal disease, meningococcal B vaccines

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INTRODUCTION

Although uncommon, invasive meningococcal disease (IMD) causes death in young healthy children and adolescents in up to 10% of cases.[1–3] Debilitating consequences frequently follow resolution of the infection, with 21–57% of cases developing long-term complications, including amputation, cerebral infarction and severe skin scarring.[4–7] The WHO estimates that there were approximately 171 000 deaths in 2000 caused by IMD.[8] A high proportion of these deaths occur in developing countries such as Africa, where traditionally the sub-Saharan 'meningitis belt' has been associated with high mortality rates from IMD caused by seasonal outbreaks due to capsular group A.

The highest incidence of IMD occurs in children below 5 years of age (particularly those under 12 months of

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age), with a second peak in adolescents and young adults 15–24 years of age.[9–12] The average annual incidence of IMD in Australia is 1:100 000,[13] and in the United Kingdom, it is 2:100 000,[14] and is higher in young infants (1.1–8.4:100 000 age-specific rate).[12] The meningococcus is carried in the nasopharynx, and IMD results following invasion of the blood or meninges by a hypervirulent strain. Adolescents have the highest prevalence of naso-pharyngeal carriage of both benign and hypervirulent meningococcal subtypes.[15]

IMD causes high anxiety in both the medical community and the general public due to its rapid onset, with the potential for a fatal outcome within 24 h of onset of infection, in previously healthy children and adolescents. Despite advances in early diagnosis and treatment with antibiotics, children remain vulnerable to IMD due to the relative immaturity of their immune system.[16]

This commentary aims to present the best available evidence for use of meningococcal vaccines in the control of IMD in children, adolescents and adults. Our literature review was confined to publications most relevant to the evaluation of IMD immunization progammes in relation to disease burden and epidemiology, meningococcal vaccine safety and efficacy, and potential programme barriers and facilitators. We identified relevant articles with searches of PubMed and Embase, and references from identified papers on these topics. Only papers published in English were included.

EPIDEMIOLOGY

There are 13 known capsular groups of *Neisseria meningitidis* identified by their different capsular polysaccharide structure; however, almost all invasive diseases are caused by six meningococcal capsular groups (A, B, C, W, Y and X).[17,18] There is a seasonal variation in disease incidence, with most cases in temperate climates occurring in winter and early spring, whereas those in sub-Saharan Africa occur during the dry season.[8,19] Viral infections, in particular, influenza, have been shown to predispose to secondary infection with meningococci.[20]

Prior to the Second World War, capsular group A meningococcal disease (MenA) was a common cause of meningococcal infection in the United Kingdom and caused a high proportion of disease in the Australian Indigenous population in the early 1970s, but is now rarely found in either country.[21–23] The reason for this decline is unknown, but it remains the most common capsular group worldwide due to the high incidence of group A disease in sub-Saharan Africa, though this is falling rapidly as a result of a targeted vaccine programme.[24] Capsular group Y is more common in some settings and causes 30% of cases in the USA.[10] Group Y is more often associated with disease in the elderly,[25] particularly in adolescents. This increase has been seen globally, including a slight increase in Australia and the United Kingdom in 2011–2012.[19,26] Capsular group W is a more common cause of IMD in Asia and Africa than in the United Kingdom and Australia, and an increasing cause of IMD in Latin America. However, recent surveillance in the United Kingdom has identified an increase in group W disease in all age groups in England and Wales, which does not appear to be related to travel or an association with pilgrimage to Hajj (historically associated with increase in cases). Capsular group X is rare and tends to cause sporadic outbreaks, the majority of which occur in Africa.[27]

Prior to the implementation of the national capsular group C meningococcal (MenC) immunization programme in the United Kingdom (November 1999) and in Australia (January 2003), one-third of the cases in both the countries were due to MenC. A large decline in the group C disease occurred following MenC vaccine introduction in both countries; however, there has been no impact on disease caused by other capsular groups including capsular group B disease.

Capsular group B disease is endemic in high and middle-income countries, including North America, Australia, South America and the European Union (EU). In Australia, 85% of the cases of IMD are now due to group B – a significant change in the serogroup epidemiology – with 65% of the cases occurring in children and adolescents.[12,19] In England and Wales, 764 cases were notified in 2011–2012, with the majority due to group B.[26] In the USA, around 30% of the cases were due to group B, and in the EU, 70% of the cases were due to group B since the introduction of MenC vaccines.[9,28]

THE BURDEN OF INVASIVE MENINGOCOCCAL DISEASE: OUTCOMES AND CONSEQUENCES

The true global burden of disease is unknown due to varying quality of surveillance systems in different regions of the world, leading to under-reporting in many countries. A study conducted in the United Kingdom prior to the introduction of a MenC vaccine, identified that 57% of the 58 cases had major physical sequelae, with greater cognitive deficits associated with younger age at diagnosis.[4] The study also found that medical follow-up was poor with only 53 of the 101 (52%) cases reporting any follow-up after IMD, with significant unrecognized and untreated morbidity. Another recent UK study –meningococcal outcome study in adolescents and children (MOSAIC) – using a case-control approach,

identified major sequelae in 36% of meningococcal survivors with a lower quality of life, greater risk of depression and poor mental health function in child and adolescent survivors of IMD compared with age and sex-matched controls.[29] Although this study provided a detailed assessment of the outcomes of IMD in the United Kingdom in children and adolescents, the burden of disease is likely to be different in different countries where different meningococcal genotypes circulate, and in the United Kingdom during different periods. In comparison, a Canadian study of IMD cases found 21% of survivors developed major sequelae.[30] The outcomes and impact from IMD in Australian children are poorly documented.[19,31–34]

In a recent audit of 10 years of IMD cases in children in South Australia, 37.6% (41/109) developed sequelae including limb amputation, hearing loss, skin scarring and chronic headaches and lethargy.[7] A long-term follow-up of survivors who had experienced bacterial meningitis in childhood was reported in the year 2000.[31] The study prospectively followed a cohort of 166 children admitted to the Royal Children's Hospital, Melbourne, between the ages of 3 months and 14 years between 1983 and 1986. This case-control study indicated 8.5% of bacterial meningitis survivors had major neurological, auditory or intellectual impairment. A further 18% of survivors had an attributable risk of minor impairment. A retrospective 5-year case-review study of IMD cases in Western Australia between 1990 and 1995 found a morbidity rate of 8.6%, with sequelae including hearing loss, limb amputation and skin scarring, and a case fatality rate of 8.6%.[34] As it is difficult to predict which children are at risk of IMD, apart from those with immunodeficiency conditions, studies have attempted to predict children that develop severe disease or sequelae.[7,35] In the recent review examining outcomes of IMD in South Australian children, those admitted with a diagnosis of meningitis and septicaemia compared to meningitis or septicaemia alone were more likely to develop sequelae [odds ratio (OR) 7.8, $P = 0.002$; OR 15.5, $P < 0.001$, respectively), with high fever on presentation to hospital a predictor of development of sequelae (OR 4.5, $P = 0.012$).[7] This study also highlighted the controversial finding that antibiotics given early prior to hospital admission may be associated with a more severe outcome, although children who receive antibiotics are likely to have more severe disease on presentation and be more easily diagnosed as a possible IMD case. A systematic review delineated the contradictory results from studies of the effects of early antibiotic treatment, suggesting confounding factors and the proportions of cases receiving antibiotics could explain the heterogeneity in results between studies.[36]

In addition to the devastating direct consequences of the disease, affected children and their families may also be compromised by the neuropsychological consequences of this infection, including depression, post-traumatic stress disorder, reduced educational attainment and inability to lead a successful and productive life.[29,37]

MENINGOCOCCAL VACCINE DEVELOPMENT

Polysaccharide meningococcal vaccines (MenACWY)

Pure polysaccharide meningococcal vaccines against disease caused by capsular groups A, C, W and Y were initially developed and derived from capsular polysaccharides of the bacteria. The capsular polysaccharide is a virulence factor for the bacteria and helps prevent immune-mediated bacterial killing. These vaccines are relatively ineffective in young children below 2 years of age, because they are unresponsive to these T-cell-independent antigens.[38] The effectiveness of these vaccines is therefore limited as the burden of disease is concentrated in the age group amongst whom these vaccines are least effective.[39] In addition, these vaccines have mostly shown no effect on nasopharyngeal carriage and therefore do not contribute to herd immunity – an important community benefit of childhood immunization programmes.[40]

Conjugate meningococcal vaccines to provide broad protection (MenC, MenA, MenACWY vaccines)

Conjugate polysaccharide vaccines have been developed in which the polysaccharide capsules are conjugated to a carrier protein to induce a T-cell-dependent response, making these vaccines immunogenic from early infancy. In the United States, a quadrivalent conjugate vaccine is recommended routinely for adolescents from 11 years of age in a two-dose schedule.[41] In Australia, the United Kingdom and other EU countries, monovalent MenC vaccines have been introduced in response to the large proportion of cases due to capsular group C in the past few decades. These MenC vaccines have been associated with a decrease in group C disease in other, unvaccinated, age groups providing evidence of the effect of conjugate vaccines on carriage and the additional benefits to the community of herd immunity. In Australia, the MenC vaccine is given as a single dose at 12 months of age, and at the time of introduction in 2003, a catch-up programme to 20 years of age was implemented. In the past few years, group C disease has rarely been reported in those aged below 20 years in Australia, and there have been only a handful of cases in older adults. In the United Kingdom, where the MenC vaccine was initially provided as a three-dose than a two-

dose infant schedule, again accompanied by a catch-up campaign incorporating adolescents and young adults, the incidence of MenC disease has decreased by 94% in immunized populations and 67% in non-immunized populations.[24,42,43] Concerns about waning of MenC antibodies in populations immunized in early childhood resulted in a booster dose being added to the infant schedule in the United Kingdom, which now consists of one dose at 3 months, a second dose at 12 months and a further dose in adolescence at 13–15 years of age.[44]

A conjugate group A vaccine was recently developed in response to the enormous disease burden from capsular group A disease in the sub-Saharan meningitis belt. A large reduction in group A disease has been observed in sub-Saharan countries that have already implemented the programme.[45,46]

Capsular group B meningococcal vaccines

Difficulties developing a group B meningococcal vaccine to provide protection against endemic strains

The development of an effective and safe capsular group B meningococcal (MenB) vaccine has been a priority in combating meningococcal disease, since this capsular group is now the predominant cause of infection in the United Kingdom, Australia and other countries. MenB vaccine development has been impeded because the group B capsular polysaccharide – a homopolymer of alpha (2–8)-linked polysialic acid – is identical to sugars decorating human foetal neural cell adhesion molecule, and therefore a human self-antigen. A capsular polysaccharide vaccine is unsuitable for vaccine development due to lack of immunogenicity (presumably as a result of tolerance to a self-antigen) and the theoretical risk of autoimmunity. When purified capsular group B polysaccharide was used to vaccinate adult volunteers, no measurable increase in anti-capsular antibody was demonstrated.[47] The use of capsular group B polysaccharide non-covalently complexed to outer membrane proteins as a human vaccine generates only short-lived IgM responses.[48] Even when conjugated to a carrier protein, it was noted to have poor immunogenicity.[49,50] Therefore, development of a conjugate MenB vaccine was not possible, and other ways to develop MenB vaccines were considered.

Development of group B meningococcal vaccines against specific group B meningococcal serosubtypes causing epidemics (e.g. MeNZB vaccine; outer membrane vesicle-based serotype-specific vaccines)

In response to the meningococcal epidemics in countries such as New Zealand and Cuba, serosubtype-specific or 'tailor-made' MenB outer membrane vesicle (OMV) vaccines were developed. The meningococcus continuously releases 'blebs' or outer membrane vesicles during development containing hundreds of different antigens.[51] These outer membrane blebs contain lipopolysaccharide (LPS) and outer membrane proteins (OMPs). In these OMVs, the OMP Porin A (PorA) is an immunodominant protein which has been shown to be immunogenic and has over 600 different variants.[52] These variants induce limited cross-protection in young children, and in this age group, any vaccine developed from OMVs tends to provide protection limited to the specific serosubtype causing the epidemic. Such vaccines were developed and implemented during long epidemics in New Zealand (MeNZB), Norway (MenBVac) and Cuba (VA-MENGOCOC-BC), caused by specific serosubtypes, but could not protect against endemic group B disease. The MeNZB vaccine, which was based on a typical isolate from the outbreak, was used in New Zealand with success,[53] but this does not provide sufficient coverage of other circulating subtypes in Australia and globally.[54] It was established early in clinical trials that immunogenicity waned and that a booster dose was important in maintaining protective antibody levels. Post-licensure surveillance of 200 000 children who received MeNZB vaccine found no increase in serious adverse event rates of pre-selected conditions (e.g. acute flaccid paralysis, encephalopathy, seizures), in excess of the background rates to be expected in the general population for these conditions.[55] Injection site reactions (redness and/or swelling) occurred more frequently in infants than in control vaccines (MenC vaccine), but were of short duration, and short-term fevers were common but comparable to those receiving the control vaccine and did not require medical intervention.[53] With more than 3 million doses of MeNZB administered to individuals under 20 years of age, no new or unexpected safety concerns were identified. More specifically, systemic events including fever were not associated with any increased risk of febrile convulsion in young children following vaccination.[56] Although the MeNZB vaccine was considered protective only against the epidemic MenB strain, there was some evidence of protection (vaccine effectiveness = 54%) against non-epidemic MenB strains.[57] The effectiveness of the New Zealand immunization programme was estimated to be 80% for children below 5 years of age[58] and 77% overall.[57]

New capsular group B meningococcal vaccines with the potential for protection against endemic disease (outer membrane vesicle and outer membrane protein-derived vaccines)

In view of the difficulties with polysaccharide vaccines against capsular group B meningococcal disease, researchers have focused on non-capsular targets in

search of candidate vaccine antigens. This, however, has been problematic due to the high level of antigenic diversity of the meningococcus.[59]

Two newly developed vaccines designed to protect against capsular group B disease (although lacking the capsular polysaccharide that defines this group) have been developed with the potential to offer protection against endemic and epidemic disease; one licensed in several countries including Australia, Canada and the EU – 4CMenB (Bexsero; Novartis Vaccines and Diagnostics, Siena, Italy) and one recently licensed in the United States – rLP2086 (Trumenba; Pfizer Vaccines, Philadelphia, Pennsylvania, USA)[60] The rLP2086 vaccine received the US Food and Drug Administration's (FDA's) Breakthrough Therapy designation (to expedite the development and review of potential new medicines for serious and life-threatening diseases),[61] which includes more intensive US FDA guidance on an efficient drug development programme.[62]

The 4CMenB vaccine

A new approach to vaccine development known as 'reverse vaccinology' identified new OMPs as potential vaccine candidates. In contrast to the traditional approaches that have been used to develop vaccines, reverse vaccinology uses the genome sequence of the bacteria to identify likely surface-exposed candidate antigens and then, after expression of the protein and preclinical immunization experiments, selects those proteins that meet set criteria as potential vaccine candidates. In the case of 4CMenB, these antigens include factor H-binding protein (fHbp), neisserial adhesion A (NadA) and neisserial heparin-binding antigen (NHBA), which were formulated with the New Zealand outbreak vaccine to produce 4CMenB. In December 2010, a file on 4CMenB was submitted to the European Medicines Agency for a marketing authorization and was assigned the trade name Bexsero.[63]

Safety and predicted effectiveness of 4CMenB: The safety and reactogenicity profile of 4CMenB was evaluated in early-phase studies, the majority of which were conducted in the United Kingdom, with a large phase 3 trial conducted in five European countries.[64,65] Studies involving over 8000 participants have shown that 4CMenB has an acceptable safety profile. Overall, reactogenicity rates amongst participants receiving 4CMenB with routine vaccines were increased compared with the rates amongst those receiving routine vaccines only or those receiving MenC and routine vaccines. Use of paracetamol to reduce the proportion and level of fever in infants and children below 2 years of age at the time of vaccination has been studied and shown to be effective, and was therefore recommended in Australia, the United Kingdom and Quebec, Canada. In contrast to a previous study that showed a reduction in immunogenicity when concomitant paracetamol was received with routine infant immunizations,[66] a phase II study of children receiving 4CMenB and routine vaccines with or without prophylactic paracetamol showed no important effect on immune response to the concomitant vaccine antigens.[67,68]

Safety data from the first population implementation of 4CMenB, in Quebec, has shown an acceptable safety profile 'in the field'. Of the 12 332 completed telephone surveys of a total of 43 740 persons aged 2 months–20 years receiving their first dose of 4CMenB, 14–15% of children below 2 years were reported as having a fever, with one febrile convulsion reported in a 1-year-old child.[69] Predicting efficacy of MenB vaccines is complicated, not only due to the low incidence of disease but also due to the number of vaccine antigens and the number of naturally occurring protein variants. When clinical efficacy trials are not feasible, appropriate surrogate markers of protection that allow interpretation of immunogenicity are therefore essential. Use of the serum bactericidal antibody (SBA) assay as a correlate of protection has been used in the case of 4CMenB, and is the licensure criterion for the vaccine. The SBA measures functional activity of antibody through complement-mediated lysis of the bacteria. This is the accepted correlate because complement-mediated bacterial killing by bactericidal antibodies is believed to be the primary mechanism of protection against meningococcal disease. The role of antibodies in natural immunity to meningococcal disease was established by Goldschneider *et al.*[70] in which case an inverse correlation between the incidence of disease and the prevalence of SBA against MenA, MenB and MenC was reported. The presence of anti-meningococcal antibodies, measured by bactericidal activity (hSBA titre $\geq$1 : 4) using an intrinsic human complement source in the assay, was indicative of protection against systemic meningococcal infection. Thus, an hSBA titre of at least 4 was used as the established end-point measurement for MenB vaccine efficacy. This approach was affirmed in 2005 at a WHO-sponsored meningococcal serology standardization workshop,[71] and from several efficacy studies of OMV vaccines.[72,73] However, an hSBA value of at least 1 : 5 was used in a number of phase 2 and 3 studies of 4CMenB, to be conservative and due to regulatory requirement.[74] Despite variation of assays between laboratories, the proportion of participants with a four-fold rise in antibodies remained relatively constant.[75] Data on SBA activity of pooled serum obtained at

approximately 13 months of age from infants immunized with three-dose priming and one-dose booster course of 4CMenB indicated 88% of a panel of 40 invasive strains in England and Wales were susceptible to killing by post-immunization sera.[76] Nevertheless, whether titres of anti-group B meningococcal bactericidal antibody correlate with true protection from meningococcal disease is unknown without a longitudinal vaccine efficacy trial. Indeed, some studies have suggested that protection against group B infection may also be due to opsonic antibodies and to innate immune responses, which are not demonstrated in the SBA.[77–80]

The 4CMenB vaccine is immunogenic against a set of four reference strains by testing hSBA responses to vaccine antigens NadA, fHbp, NHBA and NZ PorA P1.4 in infants (from 2 months of age), toddlers, adolescents and adults up to 50 years of age.[64,65,81–85] A booster dose at 1 year of age is licensed in the approved vaccination schedule for infants in Australia[86] and any child immunized under 2 years of age in the EU to support waning immunity.[74,87]

Although immunogenicity studies have demonstrated a robust immune response to 4CMenB, efficacy or effectiveness has not yet been proven as efficacy studies are unachievable due to the large number of participants required to show an effect (reduction in meningococcal disease) in view of the rarity of the disease. Strain coverage as determined by Meningococcal Antigen Testing (MATS) suggests that this vaccine could protect against 76% of circulating genotypes causing invasive meningococcal disease in Australia and 73% in England and Wales.[88,89] Predicted coverage was shown to vary between states in Australia, with coverage potentially as high as 90% in South Australia, 71% in New South Wales and 84% in Queensland, and other state coverage estimates less likely to be accurate due to the small number of samples analysed (Tasmania 45%).[90] The true effectiveness will not be known until the vaccine is used at a population level; however, the PorA component in 4CMenB is common to the MeNZB vaccine, which showed 73% effectiveness when implemented in a national immunization programme in New Zealand. In addition, the potential effect of MenB vaccines on carriage of the meningococcus in the nasopharynx is limited.[1,67,91,92] Very little is known about the effects of a MenB vaccine on carriage, but there is the potential that introduction of new MenB vaccines may disrupt the usual carriage ecosystem with non-vaccine-type replacement genotypes. Provisional results from a phase III study show 4CMenB had a modest impact on *N. meningitidis* carriage with a decrease of 16.5% in existing carriage.[93] Therefore, monitoring of clinical severity of disease and sequelae and causative genotypes will be essential prior to, during and after vaccine introduction.[19]

The rLP2086 MenB vaccine

The new MenB vaccine developed by Pfizer includes a MenB outer membrane protein, designated as LP2086, which has been shown to be a bacterial virulence factor and a target for functional bactericidal antibodies. LP2086 was subsequently determined to be fHbp which the bacterium uses to evade complement-mediated bacteriolysis and which is also contained in 4CMenB. The LP2086 amino acid sequences from MenB isolates can be divided into two sub-families – A and B – and one member from each family has been included in this vaccine to provide broad coverage against all MenB isolates. Although 4CMenB also contains this important OMP, it only contains fHbp from one sub-family, and not from both.

Clinical trials have been conducted in adolescents, children and toddlers using an initial formulation of the rLP2086 vaccine, which then underwent optimization to improve the stability of the vaccine and increase the immunogenicity.[94] The initial formulation showed robust immune responses against strains matched to the vaccine antigens, but reduced immunogenicity against divergent strains. Overall, the vaccine has been well-tolerated in clinical trials in adults, adolescents, children and toddlers.[95–97] An improved formulation of the rLP2086 has been produced and tested in adults and adolescents, with robust immune responses elicited against divergent strains.[98] Results of a small pilot study of the safety and immunogenicity of rLP2086 in 46 infants showed high fever rates, with 64 and 90% of infants developing fever after receiving one 20 or 60-μg rLP2086 dose, respectively. Only two infants in the 20-μg group and one infant in the 60-μg group experienced fevers above 39.0°C. Due to these high fever rates, the study was terminated early with the potential use of this vaccine for infants still undetermined.[99] The majority of clinical trials of the Pfizer candidate rLP2086 MenB vaccine have been conducted in Australia through a network of vaccine trials units – the National Vaccine Research Network.[94–98]

This vaccine has been developed primarily to provide protection for adolescents. Several recent MenB outbreaks in universities in the USA have confirmed the importance of having available MenB vaccines to control disease transmitted by hyper-virulent strains where young people live in close proximity.[100]

Potential additional benefits of group B meningococcal vaccines

One potential advantage of these OMP-containing MenB vaccines is the possibility that they may provide cross-protection against diseases caused by other capsular groups. As all capsular groups contain OMPs such as fHpb, an incidental benefit may be even broader protection than intended. In-vitro studies support this potential benefit.[101,102]

As suggested above, the impact of the MenB vaccine on carriage remains uncertain, but even a modest reduction in colonization rates, or colonization density, could potentially contribute to reduction in disease in unvaccinated populations.[93,103]

DISCUSSION

Vaccines are now available for the first time with the potential to provide protection against a high proportion of strains causing endemic and epidemic IMD in humans. Until recently, vaccines to provide protection against the MenA, C, W and Y have been available and funded in many countries. A vaccine to provide protection against the commonest strain (MenB) in high-income countries is now licensed and available, but not yet implemented in a national immunization programme. Although group B disease accounts for 85% of IMD cases in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC), Australia, has rejected the inclusion of 4CMenB in the National Immunization Programme Schedule for the prevention of MenB disease in infants and adolescents due to unsatisfactory cost-effective estimates.[104] The PBAC concluded the rarity of the disease does not justify the cost of a mass vaccination programme, with uncertainties around effectiveness and duration of immunity contributing to this decision. However, medical professionals and meningococcal research organizations in Australia and the United Kingdom have argued that the burden of the disease and long-term impact is not fully understood, with effectiveness unlikely to be established until the vaccine is introduced into a national programme.[105,106]

In the United Kingdom, the vaccine has borderline cost-effectiveness, with an initial analysis finding the vaccine to be just cost-effective at a very modest price,[107] a further analysis [published in an interim Joint Committee on Vaccination and Immunisation (JCVI) statement] finding it unlikely to be cost-effective,[67] and a final analysis, conducted using updated data, concluding that the vaccine could be cost-effective at a low vaccine price.[103] The UK process uses published guidance to determine cost-effectiveness and included a period of stakeholder consultation to ensure the best evidence was used to inform the cost-effectiveness model.[108]

The final position statement from the JVCI, included a recommendation to the UK Departments of Health that the MenB vaccine should be included in the funded national immunization programme, if a cost-effective price could be negotiated.[103] Acknowledged uncertainties about herd immunity, strain coverage, projected disease rates, duration of protection, costs to the health service and efficacy of 4CMenB have resulted in difficulty in evaluating the cost-effectiveness of the vaccine, essential to any funding decision.[107] Paradoxically, many of these data will only be available through use of the vaccine in large populations.[72] The success of a mass immunization campaign against group C disease in the United Kingdom has demonstrated strong evidence of high vaccine efficacy and herd immunity, with a 80% reduction in serogroup C disease within 18 months of programme implementation.[109]

Cost-effectiveness considerations of funding a group B meningococcal vaccine

Despite the difficulties with cost-effectiveness estimates, it is expected that a programme will be implemented in the United Kingdom in 2015. The final position statement from JCVI acknowledged the importance of contributions from meningitis charities and commented that 'the rapid and severe nature of IMD, the burden of disease in infants and young children and the value society places on preventing diseases in its youngest members were considered throughout the committee's deliberations'.[103] Reducing the number of vaccinations for MenB immunization, as decided by the JCVI (two primary + one booster compared to the three primary + one booster dose recommended by the manufacturer), will contribute to a more cost-effective national programme; however, there are limited data on the immunogenicity of this reduced regime. A phase 2 study comparing four doses to a single dose of 4CMenB vaccine, reported good immunogenicity after two doses at 2 and 4 months of age.[64] Reduced dose schedules have been introduced with other vaccine programmes (three doses rather than the recommended four doses of Prevenar 7/13 in the UK and Australian immunization programmes).

The availability of two licensed MenB vaccines in Australia is a much closer reality, with the second MenB vaccine being licensed in the USA very recently for use in adolescents and young adults 10–25 years of age.

There are other likely societal benefits from introduction of MenB vaccines including reduction in public anxiety and fear about IMD.

Education of parents and immunization providers about the use of MenB vaccines is important prior to introduction of a funded programme. The increased incidence of fever seen with 4CMenB could result in increased medical attention or lead to lower uptake of subsequent vaccinations, and therefore, parental and healthcare professional education about the potential reactogenicity of 4CMenB when administered with other concomitant immunizations will be important, in addition to the use of paracetamol/acetominophen. A recent study identified that despite the potential for 4CMenB to cause fever in infants, parents and the community as a whole considered the benefits of this vaccine outweighed the risks.[110] Only 10.8% [95% confidence interval (CI) 8.5–13.2] of parents reported they would be less likely to have their child immunized with a MenB vaccine due to potentially associated mild-to-moderate fever. A further study has indicated that family physicians regard the MenB vaccine for children the highest priority for a funded programme compared to currently unfunded but recommended pertussis, influenza and human papillomavirus vaccine programmes.[111]

CONCLUSION

Although eradication of the meningococcus bacteria is not achievable through vaccination and not necessarily desirable, the potential to reduce severe invasive meningococcal disease is a real possibility. There is a strong theoretical basis and early emerging evidence to suggest that these OMP-based vaccines such as the new MenB vaccines may provide not only protection against group B strains but potentially could provide cross-protection against other capsular groups. However, significant reduction in meningococcal disease is likely to require the dual approach of both an infant and adolescent immunization programme to provide protection to age groups in which the highest rates of IMD occur, and to optimize the potential herd immunity effects which have been so important in the success of conjugate meningococcal vaccines. Such an impact depends critically on the extent and duration of protection against carriage (and therefore herd immunity), which remains an unknown parameter. Furthermore, while an infant or adolescent programme could be cost-effective depending on the different modelling scenarios applied, for an adolescent programme, this would be dependent on the vaccine providing long-term protection against both disease and carriage.[112]

Surveillance of IMD following introduction of a MenB vaccine in the United Kingdom, Australia and other countries will be essential to determine how effective the vaccine is, and identify problems with increased reactogenicity, including additional healthcare utilization, any herd immune effects and any replacement disease with new virulent or non-virulent meningococcal strains emerging.

The opportunity to reduce rates of meningococcal disease is within reach and is an important consideration when prioritizing vaccines for national immunization programmes.

REFERENCES

1. Bilukha OO, Rosenstein N. National Center for Infectious Diseases (CDC), Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; 54: 1–21.
2. Peltola H. Meningococcal disease: still with us. *Rev Infect Dis* 1983; 5: 71–91.
3. Trotter CL, Chandra M, Cano R, *et al*. A surveillance network for meningococcal disease in Europe. *FEMS Microbiol Rev* 2007; 31: 27–36.
4. Borg J, Christie D, Coen PG, *et al*. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics* 2009; 123: e502–9.
5. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Hum Vaccin* 2011; 7: 458–65.
6. Karve S, Misurski D, Miller J, Davis KL. Costs of sequelae associated with invasive meningococcal disease: findings from a US managed care population. *Health Outcomes Res Med* 2011; 2: e215–26.
7. Wang B, Clarke M, Thomas N, *et al*. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. *Pediatr Infect Dis J* 2014; 33: 316–8.
8. Atkinson W. Epidemiology and prevention of vaccine-preventable diseases. Dept. of Health & Human Services, Public Health Service, Centers for Disease Control and Prevention; 2000.
9. Surveillance of invasive bacterial diseases in Europe 2008/2009. European Centre for Disease Prevention and Control, 2011, Stockholm: ECDC [viewed 21 April 2014]. <http://www.ecdc.europa.eu/en/publications/Publications/1107_SUR_IBD_2008-09.pdf>.
10. Hershey JH, Hitchcock W. Epidemiology and meningococcal serogroup distribution in the United States. *Clin Pediatr* 2010; 49: 519–24.
11. Safadi MA, Cintra OA. Epidemiology of meningococcal disease in Latin America: current situation and opportunities for prevention. *Neurol Res* 2010; 32: 263–71.
12. Chiu C, Dey A, Wang H, *et al*. Vaccine preventable diseases and vaccination coverage in Australia, 2005 to 2007. *Commun Dis Intell Q Rep* 2010; 34 (Supplement): S50–6.
13. Notification Rate of Meningococcal disease (invasive)∗, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for

2013 [database on the Internet], Department of Health and Ageing [viewed 8 November 2013]. <http://www9.health.gov.au/cda/source/rpt_4.cfm>.
14. Ladhani SN, Flood JS, Ramsay ME, *et al*. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. *Vaccine* 2012; 30: 3710–6.
15. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. *Lancet* 2007; 369: 2196–210.
16. Davies EG. The immunology of neonates and children and its relation to susceptibility to infection. Infectious diseases in the pediatric Intensive Care Unit. Berlin: Springer; 2008; 1–58.
17. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009; 27 (Suppl 2): B51–63.
18. Halperin S, Bettinger JA, Greenwood B, *et al*. The changing and dynamic epidemiology of meningococcal disease. *Vaccine* 2012; 30S: B26–36.
19. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2012. *Commun Dis Intell Q Rep* 2013; 37: E224–32.
20. Cartwright KA, Jones DM, Smith AJ, *et al*. Influenza A and meningococcal disease. *Lancet* 1991; 338: 554–7.
21. Creasey SA. Epidemic meningococcal meningitis in central Australia in the 1970s. *Med J Aust* 1991; 155: 725–6.
22. Jones D. Epidemiology of meningococcal disease in Europe and the USA. Meningococcal disease. Chichester, UK: Wiley; 1995.
23. Patel MS, Merianos A, Hanna JN, *et al*. Epidemic meningococcal meningitis in central Australia, 1987–1991. *Med J Aust* 1993; 158: 336–40.
24. Nadel S. Prospects for eradication of meningococcal disease. *Arch Dis Child* 2012; 97: 993–8.
25. Broker M, Jacobsson S, Kuusi M, *et al*. Meningococcal serogroup Y emergence in Europe: update 2011. *Hum Vaccin Immunother* 2012; 8: 1907–11.
26. Public Health England. Invasive meningococcal infections (England and Wales): annual report for 2011/12. Health Protect Rep 2013; 7:18–22.
27. Boisier P, Nicolas P, Djibo S, *et al*. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. *Clin Infect Dis* 2007; 44: 657–63.
28. Active Bacterial Core Surveillance Report. Emerging infections program network, *Neisseria meningitidis*, Centers for Disease Control and Prevention, 2012 [viewed 21 April 2014]. <http://www.cdc.gov/abcs/reports-findings/surv-reports/mening12.html>.
29. Viner RM, Booy R, Johnson H, *et al*. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol* 2012; 11: 774–83.
30. Bettinger JA, Scheifele DW, Le Saux N, *et al*. Members of Canadian Immunization Monitoring Program, Active (IMPACT). The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J* 2013; 32: e20–5.
31. Grimwood K, Anderson VA, Bond L, *et al*. Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics* 1995; 95: 646–56.
32. Guimont C, Hullick C, Durrheim D, *et al*. Invasive meningococcal disease: improving management through structured review of cases in the Hunter New England area, Australia. *J Public Health (Oxf)* 2010; 32: 38–43.
33. Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971–1980. *J Hyg (Lond)* 1983; 90: 49–54.
34. Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health* 1999; 35: 42–48.
35. de Jonge RC, van Furth AM, Wassenaar M, *et al*. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infect Dis* 2010; 10: 232.
36. Hahne SJ, Charlett A, Purcell B, *et al*. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *Br Med J (Clin Res ed)* 2006; 332: 1299–303.
37. Garralda ME, Gledhill J, Nadel S, *et al*. Longer-term psychiatric adjustment of children and parents after meningococcal disease. *Pediatr Crit Care Med* 2009; 10: 675–80.
38. Borrow R, Goldblatt D, Andrews N, *et al*. Influence of prior meningococcal C polysaccharide vaccination on the response and generation of memory after meningococcal C conjugate vaccination in young children. *J Infect Dis* 2001; 184: 377–80.
39. Gold R, Lepow ML, Goldschneider I, Draper TL, Gotschlich EC. Clinical evaluation of group A and group C meningococcal polysaccharide vaccines in infants. *J Clin Invest* 1975; 56: 1536–47.
40. Dellicour S, Greenwood B. Systematic review: Impact of meningococcal vaccination on pharyngeal carriage of meningococci. *Trop Med Int Health* 2007; 12: 1409–21.
41. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): prevention and control of meningococcal disease. *Morb Mortal Wkly Rep* 2013; 62: 14.
42. Ramsay ME, Andrews NJ, Trotter CL, *et al*. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *Br Med J (Clin Res ed)* 2003; 326: 365–6.
43. Campbell H, Andrews N, Borrow R, *et al*. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clin Vaccine Immunol* 2010; 17: 840–7.
44. Changes to the meningococcal C conjugate (MenC) vaccine schedule 2013 to 2014: advice for healthcare professionals. London: Department of Health; 2014 [cited 21 April 2014].

45. Collard JM, Issaka B, Zaneidou M, *et al*. Epidemiological changes in meningococcal meningitis in Niger from 2008 to 2011 and the impact of vaccination. *BMC Infect Dis* 2013; 13: 576.
46. Daugla DM, Gami JP, Gamougam K, *et al*. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014; 383: 40–7.
47. Wyle FA, Artenstein MS, Brandt BL, *et al*. Immunologic response of man to group B meningococcal polysaccharide vaccines. *J Infect Dis* 1972; 126: 514–21.
48. Zollinger WD, Mandrell RE, Griffiss JM, *et al*. Complex of meningococcal group B polysaccharide and type 2 outer membrane protein immunogenic in man. *J Clin Invest* 1979; 63: 836–48.
49. Finne J, Leinonen M, Makela PH. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. *Lancet* 1983; 2: 355–7.
50. Zollinger WD, Moran EE, Devi SJ, Frasch CE. Bactericidal antibody responses of juvenile rhesus monkeys immunized with group B *Neisseria meningitidis* capsular polysaccharide-protein conjugate vaccines. *Infect Immun* 1997; 65: 1053–60.
51. Williams JN, Skipp PJ, Humphries HE, *et al*. Proteomic analysis of outer membranes and vesicles from wild-type serogroup B *Neisseria meningitidis* and a lipopolysaccharide-deficient mutant. *Infect Immun* 2007; 75: 1364–72.
52. Devoe IW, Gilchrist JE. Release of endotoxin in the form of cell wall blebs during in vitro growth of *Neisseria meningitidis*. *J Exp Med* 1973; 138: 1156–67.
53. Oster P, Lennon D, O'Hallahan J, *et al*. MeNZB: a safe and highly immunogenic tailor-made vaccine against the New Zealand *Neisseria meningitidis* serogroup B disease epidemic strain. *Vaccine* 2005; 23: 2191–6.
54. Tapsall J. Annual report of the Australian Meningococcal Surveillance Programme, 2007 – Amended. *Commun Dis Intell Q Rep* 2009; 33: 1–9.
55. Holst J, Oster P, Arnold R, *et al*. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. *Hum Vaccin Immunother* 2013; 9: 1241–53.
56. McNicholas A, Galloway Y, Stehr-Green P, *et al*. Post-marketing safety monitoring of a new group B meningococcal vaccine in New Zealand, 2004–2006. *Hum Vaccin* 2007; 3: 196–204.
57. Arnold R, Galloway Y, McNicholas A, O'Hallahan J. Effectiveness of a vaccination programme for an epidemic of meningococcal B in New Zealand. *Vaccine* 2011; 29: 7100–6.
58. Galloway Y, Stehr-Green P, McNicholas A, O'Hallahan J. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years. *Int J Epidemiol* 2009; 38: 413–8.
59. Bai X, Borrow R. Genetic shifts of *Neisseria meningitidis* serogroup B antigens and the quest for a broadly cross-protective vaccine. *Expert Rev Vaccines* 2010; 9: 1203–17.
60. Food and Drug Administration. Vaccines, bloods and biologics; Trumenba [viewed 3 November 2014]. <http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm421020.htm>.
61. Food and Drug Administration Safety and Innovation Act. U.S. Food Drug Administration, 2012 [viewed 15 April 2014]. <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>.
62. Frequently asked questions: breakthrough therapies. U.S. Food Drug Administration, 2014 [viewed 15 April 2014]. <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm341027.htm>.
63. Bai X, Findlow J, Borrow R. Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles. *Expert Opin Biol Ther* 2011; 11: 969–85.
64. Findlow J, Borrow R, Snape MD, *et al*. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin Infect Dis* 2010; 51: 1127–37.
65. Vesikari T, Esposito S, Prymula R, *et al*. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet* 2013; 381: 825–35.
66. Prymula R, Siegrist CA, Chlibek R, *et al*. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet* 2009; 374: 1339.
67. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health, 24 July 2013 [viewed 2 September 2013]. <https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk>.
68. Prymula R, Esposito S, Zuccotti GV, *et al*. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I): effects of prophylactic paracetamol on immunogenicity and reactogenicity of routine infant vaccines and 4CMenB. *Hum Vaccin Immunother* 2014; 10: 1993–2004.
69. Rapport interimaire de surveillance de la securite de la premiere dose du vaccine contre le meningocoque de serogroup B au Saguenay-Lac-Saint-Jean. Institut national de sante publique du Quebec [viewed 9 November 2014]. <http://www.inspq.qc.ca/pdf/publications/1885_Vaccin_Menincogoque_SerogroupeB.pdf>.
70. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med* 1969; 129: 1307–26.

71. Borrow R, Carlone GM, Rosenstein N, *et al*. *Neisseria meningitidis* group B correlates of protection and assay standardization–international meeting report Emory University, Atlanta, Georgia, United States, 16–17 March 2005. *Vaccine* 2006; 24: 5093–107.
72. Bjune G, Gronnesby JK, Hoiby EA, *et al*. Results of an efficacy trial with an outer membrane vesicle vaccine against systemic serogroup B meningococcal disease in Norway. *NIPH Ann* 1991; 14: 125–30; discussion 30–2.
73. Holst J, Feiring B, Fuglesang JE, *et al*. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine* 2003; 21: 734–7.
74. Martin NG, Snape MD. A multicomponent serogroup B meningococcal vaccine is licensed for use in Europe: what do we know, and what are we yet to learn? *Expert Rev Vaccines* 2013; 12: 837–58.
75. Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection: serum bactericidal antibody activity. *Vaccine* 2005; 23: 2222–7.
76. Frosi G, Biolchi A, Lo Sapio M, *et al*. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; 31: 4968–74.
77. Lehmann AK, Halstensen A, Naess A, *et al*. Immunization against serogroup B meningococci. Opsonin response in vaccinees as measured by chemiluminescence. *APMIS* 1991; 99: 769–72.
78. Lehmann AK, Halstensen A, Aaberge IS, *et al*. Human opsonins induced during meningococcal disease recognize outer membrane proteins PorA and PorB. *Infect Immun* 1999; 67: 2552–60.
79. Lehmann AK, Gorringe AR, Reddin KM, *et al*. Human opsonins induced during meningococcal disease recognize transferrin binding protein complexes. *Infect Immun* 1999; 67: 6526–32.
80. Ison CA, Anwar N, Cole MJ, *et al*. Assessment of immune response to meningococcal disease: comparison of a whole-blood assay and the serum bactericidal assay. *Microb Pathog* 1999; 27: 207–14.
81. Gossger N, Snape MD, Yu LM, *et al*. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *J Am Med Assoc* 2012; 307: 573–82.
82. Snape MD, Dawson T, Oster P, *et al*. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. *Pediatr Infect Dis J* 2010; 29: e71–9.
83. Santolaya ME, O'Ryan ML, Valenzuela MT, *et al*. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet* 2012; 379: 617–24.
84. Kimura A, Toneatto D, Kleinschmidt A, *et al*. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine and a quadrivalent meningococcal CRM197 conjugate vaccine against serogroups A, C, W-135, and Y in adults who are at increased risk for occupational exposure to meningococcal isolates. *Clin Vaccine Immunol* 2011; 18: 483–6.
85. Toneatto D, Ismaili S, Ypma E, *et al*. The first use of an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) in humans. *Hum Vaccines* 2011; 7: 646–53.
86. Australian Technical Advisory Group on Immunisation. Advice for immunisation providers regarding the use of Bexsero®: a recombinant multicomponent meningococcal B vaccine (4CMenB). Australian Government Department of Health, 2014 [viewed 21 April 2014]. <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/85A6879534C02B4DCA257B640002F38E/$File/ATAGI-advice-bexsero.pdf>.
87. Summary of Product Characteristics: Bexsero Meningococcal Group B vaccine for injection in pre-filled syringe. eMC, 02 December 2013 [viewed 21 April 2014]. <http://www.medicines.org.uk/emc/medicine/28407/SPC/Bexsero+Meningococcal+Group+B+vaccine+for+injection+in+pre-filled+syringe/>.
88. Tozer SJ, Whiley DM, Smith HV, *et al*. Use of the meningococcal antigen typing system (MATS) to assess the Australian meningococcal strain coverage with 4CMenB serogroup b vaccine. 27th Congress of the International Pediatric Association, 28 August 2013; Melbourne, Australia.
89. Vogel U, Taha MK, Vazquez JA, *et al*. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. *Lancet Infect Dis* 2013; 13: 416–25.
90. Serruto D, Bambini S, Tomita T, *et al*. Use of the Meningococcal Antigen Typing System (MATS) to assess Australian epidemiology and meningococcal strain coverage with a multicomponent serogroup B vaccine. International Congress of Paediatrics, Melbourne, Australia; 2013.
91. Bjune G. 'Herd immunity' and the meningococcal vaccine trial in Norway. *Lancet* 1992; 340: 315.
92. Perkins BA, Jonsdottir K, Briem H, *et al*. Immunogenicity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among young adults in Iceland. *J Infect Dis* 1998; 177: 683–91.
93. Read RC, Baxter D, Chadwick DR, *et al*. Impact of a quadrivalent conjugate (MenACWY-CRM) or a serogroup B (4CMenB) meningococcal vaccine on meningococcal carriage in English university students. 31st Annual Meeting of the European Society of Paediatric Infectious Diseases. Milan, Italy; 2013.
94. Marshall HS, Richmond PC, Nissen MD, *et al*. Safety and immunogenicity of a meningococcal B bivalent rLP2086 vaccine in healthy toddlers aged 18-36 months: a phase 1 randomized-controlled clinical trial. *Pediatr Infect Dis J* 2012; 31: 1061–8.

95. Marshall HS, Richmond PC, Nissen MD, *et al*. A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults. *Vaccine* 2013; 31: 1569–75.
96. Richmond PC, Nissen MD, Marshall HS, *et al*. A bivalent *Neisseria meningitidis* recombinant lipidated factor H binding protein vaccine in young adults: results of a randomised, controlled, dose-escalation phase 1 trial. *Vaccine* 2012; 30: 6163–74.
97. Nissen MD, Marshall HS, Richmond PC, *et al*. A randomized, controlled, phase 1/2 trial of a *Neisseria meningitidis* serogroup B bivalent rLP2086 vaccine in healthy children and adolescents. *Pediatr Infect Dis J* 2013; 32: 364–71.
98. Richmond PC, Marshall HS, Nissen MD, *et al*. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis* 2012; 12: 597–607.
99. Martinon-Torres F, Gimenez-Sanchez F, Bernaola-Iturbe E, *et al*. A randomized, phase $^{1}/_{2}$ trial of the safety, tolerability, and immunogenicity of bivalent rLP2086 meningococcal B vaccine in healthy infants. *Vaccine* 2014; 32: 5206–11.
100. Serogroup B meningococcal vaccine and outbreaks. Centers for Disease Control and Prevention [viewed 4 April 2014]. <http://www.cdc.gov/meningococcal/outbreaks/vaccine-serogroupB.html>.
101. Hong E, Giuliani MM, Deghmane AE, *et al*. Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control *Neisseria meningitidis* capsular group X outbreaks in Africa? *Vaccine* 2013; 31: 1113–6.
102. Claus H, Borrow R, Taha M-K, *et al*. Potential coverage of the 4CMenB vaccine in non-B meningococci. 18th International Pathogenic Neisseria Conference. Wurzburg, Germany; 2012.
103. JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health, 21 March 2014 [viewed 4 April 2014]. <https://www.gov.uk/government/publications/meningococcal-b-vaccine-jcvi-position-statement>.
104. November 2013 PBAC Meeting Outcomes – '1st time' decisions not to recommend. Canberra: Department of Health, 2013 [viewed 20 January 2014]. <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes>.
105. Patients want 'compassion' on meningococcal vaccine. PharmaDispatch; 15 January 2014 [viewed 20 January 2014]. <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>.
106. Head C. Immunisation against meningococcus B. *Lancet* 2013; 382: 935.
107. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine* 2013; 31: 2638–46.
108. Minute of the meeting on 11th/12th February 2014. London: Department of Health, 2014 [viewed 16 April 2014]. <https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation>.
109. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* 2001; 20 (Suppl 1): S58–67.
110. Marshall H, Clarke M, Sullivan T. Parental and community acceptance of the benefits and risks associated with meningococcal B vaccines. *Vaccine* 2014; 32: 338–44.
111. Taylor K, Stocks N, Marshall H. The missing link: family physician perspectives on barriers and enablers to prescribing non-funded vaccines. *Vaccine* 2014; 32: 4214–9.
112. Pollard AJ, Riordan A, Ramsay M. Group B meningococcal vaccine: recommendations for UK use. *Lancet* 2014; 383: 1103–4.

3.2 LIFETIME COSTS: A MARKOV MODEL

Based on a review of the literature, it was found that no studies estimated direct non-healthcare costs representing the cost to patients and the government (e.g. transportation, special education), productivity loss representing the cost to society (e.g. reduced employment fraction) and long-term healthcare costs associated with IMD. The cost of illness (COI) studies can help policy makers and researchers to understand the financial impact of IMD on the patients, their families, the healthcare system and society. The COI study can provide estimates of the potential cost savings that might result from preventative programs (e.g. meningococcal vaccination) to inform cost-effectiveness analyses.

A cohort-based state-transition (Markov) model was developed to predict the average lifetime cost of IMD. The best available published evidence was used to populate the model. A manuscript titled “Lifetime costs of invasive meningococcal disease: A Markov model approach” has been prepared for publication and will be submitted to the journal “Vaccine”.

3.2.1 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Lifetime costs of Invasive Meningococcal Disease: A Markov model approach
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Wang B, Haji Ali Afzali H, Giles L, Marshall H. Understanding the lifetime costs of Invasive Meningococcal Disease: A Markov model approach

Principal Author

Name of Principal Author (Candidate)	Bing Wang		
Contribution to the Paper	BW conceived and designed the study, developed the costing model, and produced the first draft of the manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	03 OCT 2018

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Hossein Haji Ali Afzali		
Contribution to the Paper	HHAA conceived and designed the study, instructed BW in model development, and contributed to, reviewed and edited the manuscript.		
Signature		Date	9/10/2018

Name of Co-Author	Lynne Giles		
Contribution to the Paper	LG contributed to, reviewed, and edited the manuscript.		
Signature		Date	9/10/18

Name of Co-Author	Helen Marshall		
Contribution to the Paper	HM conceived and designed the study, and contributed to, reviewed and edited the manuscript.		
Signature		Date	04 OCT 2018

Please cut and paste additional co-author panels here as required.

3.2.2 PUBLICATION

Editor-in-Chief

Vaccine

22 February 2019

Dear Editor-in-Chief,

On behalf of my co-authors, I am pleased to submit to the journal, Vaccine, our manuscript entitled: **Lifetime costs of invasive meningococcal disease: A Markov model approach.**

Understanding the financial costs of invasive meningococcal disease (IMD) is an important step in developing health economic models for preventative health programs such as immunisation. To our knowledge, no cost of illness studies have estimated costs associated with IMD by using health economic modelling techniques to provide information for healthcare resource prioritising.

All authors acknowledge that this paper has no prior publications or submissions with any overlapping information. The work is not and will not be submitted to any other journal while under consideration by Vaccine. This paper is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. All authors acknowledge that the article has not been published previously, and it is not under consideration for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and there are no other persons who satisfied the

criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all authors. Authors prefer to have figures published in black and white at no additional cost.

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Title: Lifetime costs of invasive meningococcal disease: A Markov model approach

Key words: meningococcal disease, costs, Markov model

Running title: Lifetime costs of meningococcal disease

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Key Points:

Invasive meningococcal disease (IMD) is a public health concern worldwide. A mathematical model was constructed to predict lifetime costs of IMD. The burden of IMD is substantial with significant healthcare costs incurred in young patients and patients with sequelae.

Abstract

Background. Invasive meningococcal disease (IMD) is an uncommon but life-threatening infectious disease associated with high sequelae rates in young children and an increased risk of mortality in adolescents and young adults. Funding decisions to reject inclusion of new meningococcal serogroup B vaccines on national immunisation schedules have been criticised by IMD patients, their families, paediatricians and charity organisations. We aim to estimate the lifetime costs of IMD with the best available evidence to inform cost-effectiveness analyses.

Methods. A Markov model was developed taking healthcare system and societal perspectives. A range of data including age-specific mortality rates, and probabilities of IMD-related sequelae were derived from a systematic review and meta-analysis. All currencies were inflated to year 2017 prices by using consumer price indexes in local countries and converted to US dollars by applying purchasing power parities conversion rates.

Results. The estimated lifetime societal cost is US$319,896.74 per IMD case including the direct healthcare cost of US$65,035.49. Using a discount rate of 5%, the costs are US$54,278.51 and US$13,968.40 respectively. Chronic renal failure and limb amputation result in the highest direct healthcare costs per patient. Patients aged <5 years incur the higher healthcare expenditure compared with other age groups. The costing results are sensitive to the discount rate, disease incidence, acute admission costs, and sequelae rates and costs of brain injuries and epilepsy.

Conclusions. IMD can result in substantial costs to the healthcare system and society. Understanding the costs of care can assist decision-making bodies in evaluating cost-effectiveness of new vaccine programs.

Introduction

Although invasive meningococcal disease (IMD) is uncommon, the disease causes major public health and societal concerns due to its rapid onset and potentially severe or life-threatening outcomes. Despite advanced clinical management, the disease is still associated with a high disability rate in young children and an increased mortality risk in adolescents and young adults. Up to 58% of adolescents develop sequelae [1] and 9% of young patients have major disabling deficits after the disease [2]. Case fatality rates (CFRs) vary between 5 and 20% [3].

Vaccines are available to protect against five major serogroups: A, B, C, W and Y. New meningococcal serogroup B (MenB) vaccine programs are publicly funded in a limited number of countries or states (e.g. UK, Ireland, Italy and South Australia). Meningococcal serogroup ACWY vaccines have been added to national immunisation schedules or are being considered by national funding bodies in several countries due to the continuing rapid rise in serogroup W disease. Although guidelines developed by funding bodies (e.g. Australia and UK) consider factors such as disease severity and rarity, economic evaluation is one of the key inputs that inform decisions on whether to publicly fund new meningococcal vaccine strategies.

Cost of illness (COI) studies can provide important baseline information for future cost-effectiveness analyses [4]. COI results help policy-makers understand the financial impact of IMD on the healthcare system and the potential lifetime cost savings that might arise from new meningococcal vaccine programs [5,6]. Previous costing studies estimating IMD direct healthcare costs were conducted in the US and Australia, but the financial impact of long-term care associated with IMD disabilities were not investigated [7-10]. Although lifetime costs were estimated in a COI study [11] and several case

studies by using two hypothetical cases of severe meningococcal meningitis and septicaemia [12-14], decision analytic models (e.g. Markov models) are required to capture all important healthcare and societal costs over a lifetime. Such models predict the experience of health states that are likely to be experienced by the patient, often over the lifetime of a study population. Costs are then applied to the time spent in different health states to estimate lifetime costs.

Decision analytic models have been used to assess cost-effectiveness of meningococcal vaccines [15-26]. However, few studies fully justified the choice of model structure (representing health states included in the model) and approaches to systematically identify the best available evidence to populate the model. It is well noted that the choice of inappropriate model structure, even if we use the true value of inputs, can lead to biased model predictions and, hence, poorly informed policy decisions [27]. Some model-based studies of IMD vaccines excluded important health states such as renal failure or speech/communication problems [15-17,20]. Recent guidelines for good modelling practice highlight the need for the development of a conceptual model (reflecting the current clinical understanding of the condition under study) as a basis for defining the structure of cost-effectiveness models [28]. In terms of populating processes, it was found that wide-ranging parameter values (e.g. sequelae rates varied from 13% [17] to 77% [22]) were extracted from the published literature and used in these models. Modelling results are sensitive to the choice of model inputs and structure. Two prior modelling studies estimated the rate of cognitive problems as 23-25% [18,22] based on a follow-up study in Iceland. However, the rate of cognitive dysfunction was reported as 1.5% in the original retrospective study [29]. Furthermore, societal costs associated with long-term disabilities and premature death have been considered substantial [30], but some evaluations focused solely on direct healthcare costs [20,22,24,26].

Our study therefore aims to address these issues to further improve the estimation of the lifetime cost associated with IMD from healthcare system and societal perspectives. Following recent guidelines for good modelling practice [28,31,32], we report on the use of a conceptual framework of the progression of IMD to guide the development of a Markov model to predict IMD costs to a maximum age of 100 years.

Methods

A Markov model with yearly cycles was built using TreeAge Pro (version 2018 R2.0). In the base case, future costs were discounted to their present value at 5% annually and the healthcare system perspective was employed as recommended by Australian guidelines [33].

The healthcare system perspective captures direct medical costs associated with IMD and public health management. The analysis was also performed from the societal perspective, including direct healthcare costs, direct non-healthcare costs (e.g. home modification and special education) and indirect costs associated with productivity loss.

Based on the number of births registered in Australia in 2016, a hypothetical birth cohort of 311,104 newborns was followed over a 100-year time horizon. All costs were inflated to price year 2017 based on the Consumer Price Indexes in local countries and converted to US dollars using Purchasing Power Parities [34].

Model structure

To inform model structure, we systematically reviewed clinical and health economics literature published after 2000, documenting disease progression and important health states associated with IMD. Based on clinical and health economic literature review, we drafted a conceptual framework (Supplementary Figure 1).

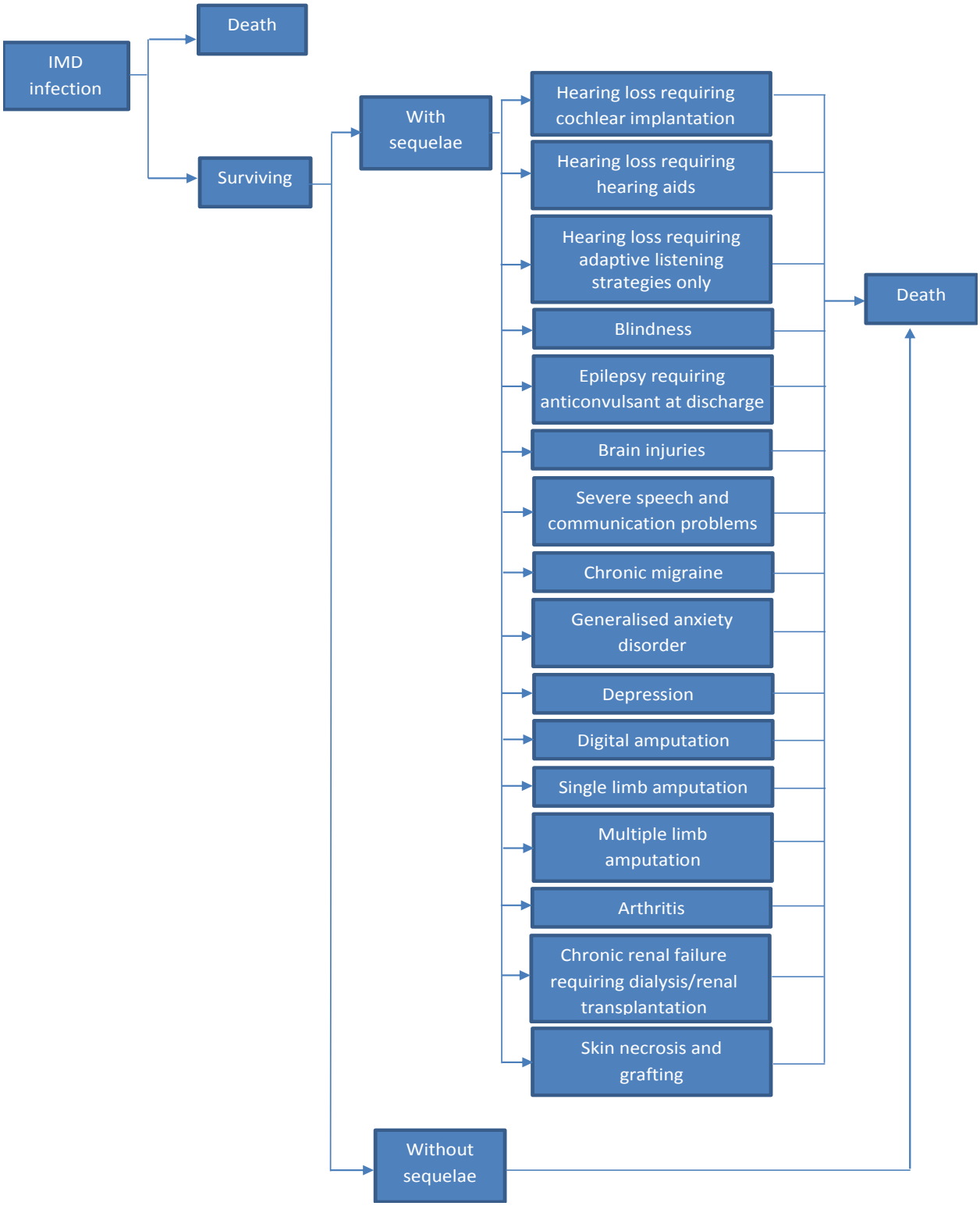
To further guide the development of model structure, four clinical consultants in immunisation, paediatrics, infectious diseases, and paediatric rehabilitation, two experts in public health, two senior researchers working in the field of IMD, and a health economist were invited to be part of an advisory meeting, in which a focus group

discussion was conducted to obtain expert opinions on likelihood and importance of sequelae. Experts were also asked to complete a questionnaire following the discussion (Supplementary Table 1).

The main structure of the draft conceptual model was agreed by the expert panel. Based on the discussion, hearing impairments, amputation and renal failure were further disaggregated. The rating results were used to assist in excluding health states. We further excluded hepatic dysfunction from the model due to low probability and impact scores derived from the questionnaires (a mean likelihood score ≤3 and all mean impact scores ≤3).

Owing to a low probability and limited data availability, two health states, bone and joint diseases and vasculitis, were removed from the final conceptual framework (Supplementary Figure 2) to develop the final costing model (Figure 1). Based on data availability, motor deficits, cognitive impairments and other neurological impairments were aggregated into one health state, brain injuries. Social functioning problems were specified as severe speech and communication problems. Psychological problems were separated into two health states: depression and generalised anxiety disorder.

Figure 1 Revised model structure



Model inputs and assumptions

We assumed all IMD cases would be hospitalised. As IMD was associated with an increased risk of death due to nervous system diseases (mortality rate ratio (MRR): 3.15) and genitourinary diseases (MRR: 6.26) [34], IMD patients with brain injuries and chronic renal failure were assumed to have a higher probability of death. As recurrent IMD is rare [36], each survivor would not have recurrent IMD. Ages of onset of generalised anxiety disorder and depression are 6 and 13 years, respectively [37].

Epidemiological/clinical inputs

A systematic review was performed to identify probabilities of health states. Sequelae/complications reported in the literature were highly heterogeneous, as study populations, sequelae definitions, study design and follow-up periods varied significantly between studies. Therefore, we did not synthesise clinical evidence. Clinical data reported in studies with small sample sizes (n<100) were excluded from data identification, as studies with small sample sizes might produce low quality results with wide variance [38]. We only included studies conducted in developed countries (e.g. UK, US, Australia, etc.) due to applicability issues. Twenty-two studies were used to select clinical parameters (Supplementary Table 2). If more than one study reported a specific sequela rate, the value of the sequelae rate was determined based on the quality of studies (study limitations and imprecision) as suggested by GRADE criteria [39] (Supplementary Table 3).

The disease incidence was determined using Australian notification data in 2017. The national life table in the 2014-2016 period was used to predict non-meningococcal mortality after removing premature deaths caused by IMD. The CFRs presented in national surveillance reports in Australia used two different datasets. Those datasets

were not linked. The CFRs were relatively lower than other developed countries. Therefore, we used age-specific CFRs derived from a systematic review and meta-analysis (manuscript in preparation).

Cost inputs

Direct healthcare costs associated with admissions, rehabilitation, outpatient visits and prostheses were included (Supplementary Table 4). The costs associated with acute admissions were derived from the National Hospital Cost Data Collection reports between 2013 and 2016. Direct healthcare costs relevant to amputations, stump revisions and skin scars were estimated by using cost weights for Australian Refined Diagnosis Related Groups (AR-DRGs). Due to a lack of costing data pertaining to long-term disabilities, costs associated with sequelae were derived from COI studies describing the cost burden on similar medical conditions. A targeted literature search was performed to identify cost parameters. It was assumed that 15% of primary amputations performed before 12 years of age would have two stump revisions at a three year interval [40-43].

Direct non-healthcare costs associated with long-term care, informal carers, early intervention/special education, home/vehicle modification, and/or personal out-of-pocket costs were included (Supplementary Table 4).

To estimate indirect costs, two approaches were used: human capital (HC) and friction cost (FC) methods [44]. The HC method estimates the reduction in gross earnings due to morbidity and/or premature mortality. The FC method only considers the time span employers need to restore the initial production level [45].

A friction period of 3 months was used for premature death caused by IMD [46,47]. We also considered a friction period of 1.5 months for patients with blindness, brain injuries, multiple limb amputation and renal failure [19].

By using the HC method, the productivity loss associated with acute admissions for patients without sequelae was estimated by multiplying national average weekly income and an average length of stay in hospital [15]. For patients with sequelae, three additional days plus an average length of hospital stay were considered due to the severity of the disease. The value of lifetime income foregone due to premature death was calculated on an annual basis from the age of death to the retirement age using age-specific wage weighted by age-specific employment rate.

Model validation

Three clinical consultants in infectious diseases or paediatrics (not involved in the model development process) were invited to investigate the model's face validity regarding the model structure, model inputs, assumptions and results. A focus group discussion was conducted. They concluded the lifetime costs generated from our model were highly likely to be underestimated. To address this concern, we further investigated onset ages of depression/generalised anxiety disorder and economic parameter values relevant to amputation and severe speech problems. The onset ages of depression/generalised anxiety disorder were revised based on a large survey study in the US [37]. The costs associated with amputation and severe speech problems were revised after interviewing a paediatric rehabilitation consultant, senior speech pathologist and senior prosthetist/orthotist. The costs associated with prostheses, surgical revisions and rehabilitation services were considered for patients with amputation.

Verification was performed by BW and HHAA independently to examine and confirm whether all equations and parameters populated the model correctly. External validity was checked through comparison of population figures predicted in the model against the Australian population in 2016. Cross validation of our final model was assessed by comparing costing results with previous modelling studies.

Sensitivity analyses

One-way sensitivity analyses were conducted to test the sensitivity of the base case model predictions to model inputs. Australian historically low and high incidence rates in 2013 and 2002 respectively, and 95% confidence intervals of CFRs were used. Due to lack of estimates of precision (e.g. confidence intervals), all other model inputs were varied between 75% and 125% of their point estimates. Discount rates of 0%, and 5% were also considered in the analyses.

Results

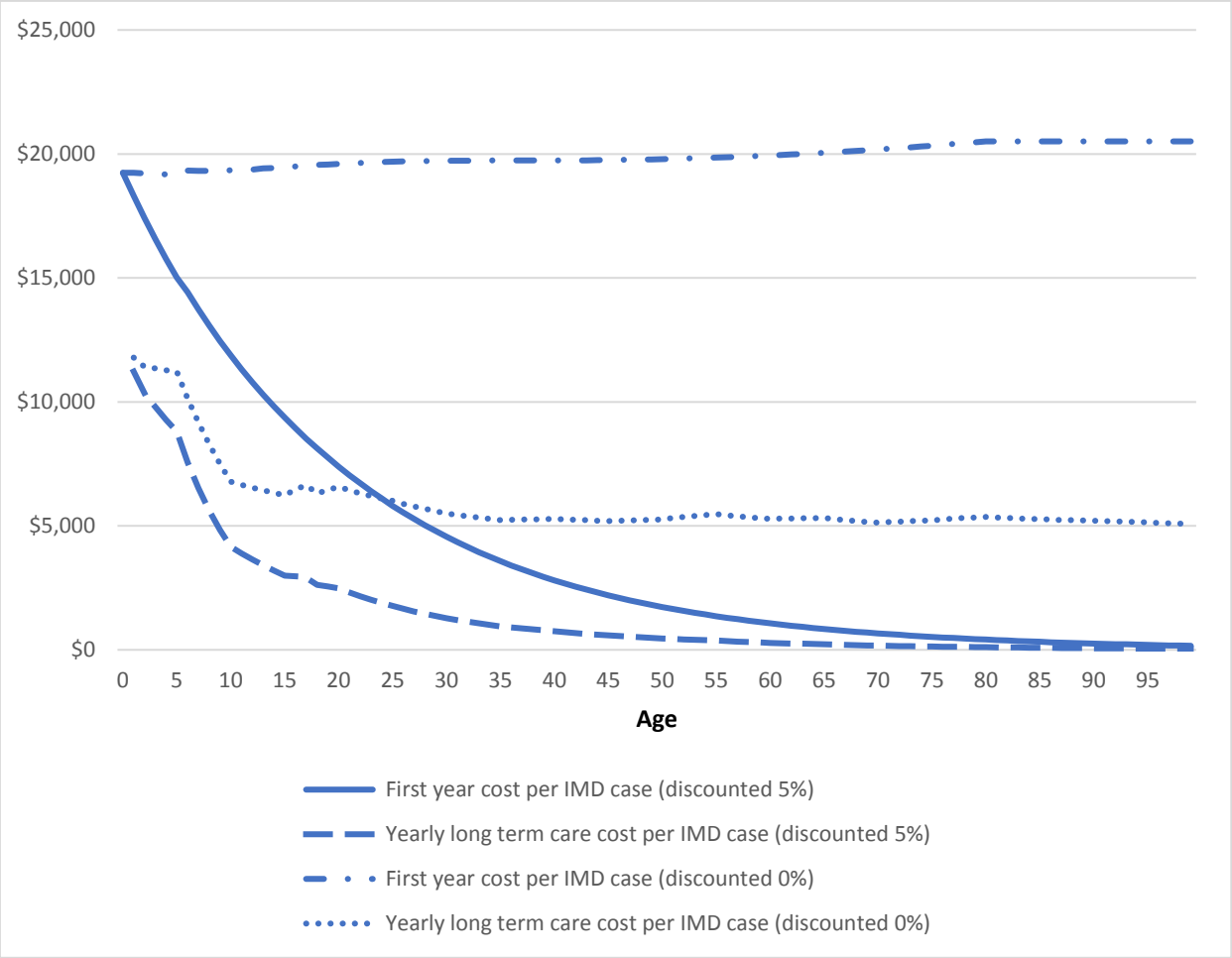
The model predicted 419 IMD cases with a total direct healthcare cost of US$5,860,991.21 (discounted at 5%) or US$27,288,190.17 (no discounting) after following a birth cohort of 311,104 newborns over the model's 100-year horizon (Table 1). The expected direct healthcare cost per IMD case is US$13,968.40 (discounted at 5%) or US$65,035.49 (no discounting) over a lifetime. The societal cost estimate using HC method is much higher than the estimate using FC methods.

Table 1 lifetime costs per IMD case (US$) estimated from the healthcare system and societal perspectives and discounted at 5, 3.5 and 0%

Discount rate	Direct healthcare cost	Societal cost (HC method)	Societal cost (FC method)
5%	$13,968.40 **(base case)**	$54,278.51	$24,109.56
3.5%	$19,072.94	$84,189.32	$32,066.91
0%	$65,035.49	$319,896.74	$96,809.26

With a discount rate of 5%, the first-year healthcare cost is US$19,236.91 in patients aged one and decrease gradually by age (Figure 2). For patients with disabilities requiring long term care, the average clinical follow-up cost is estimated to be US$11,225.79 for children aged two and has shown a steady decline by age.

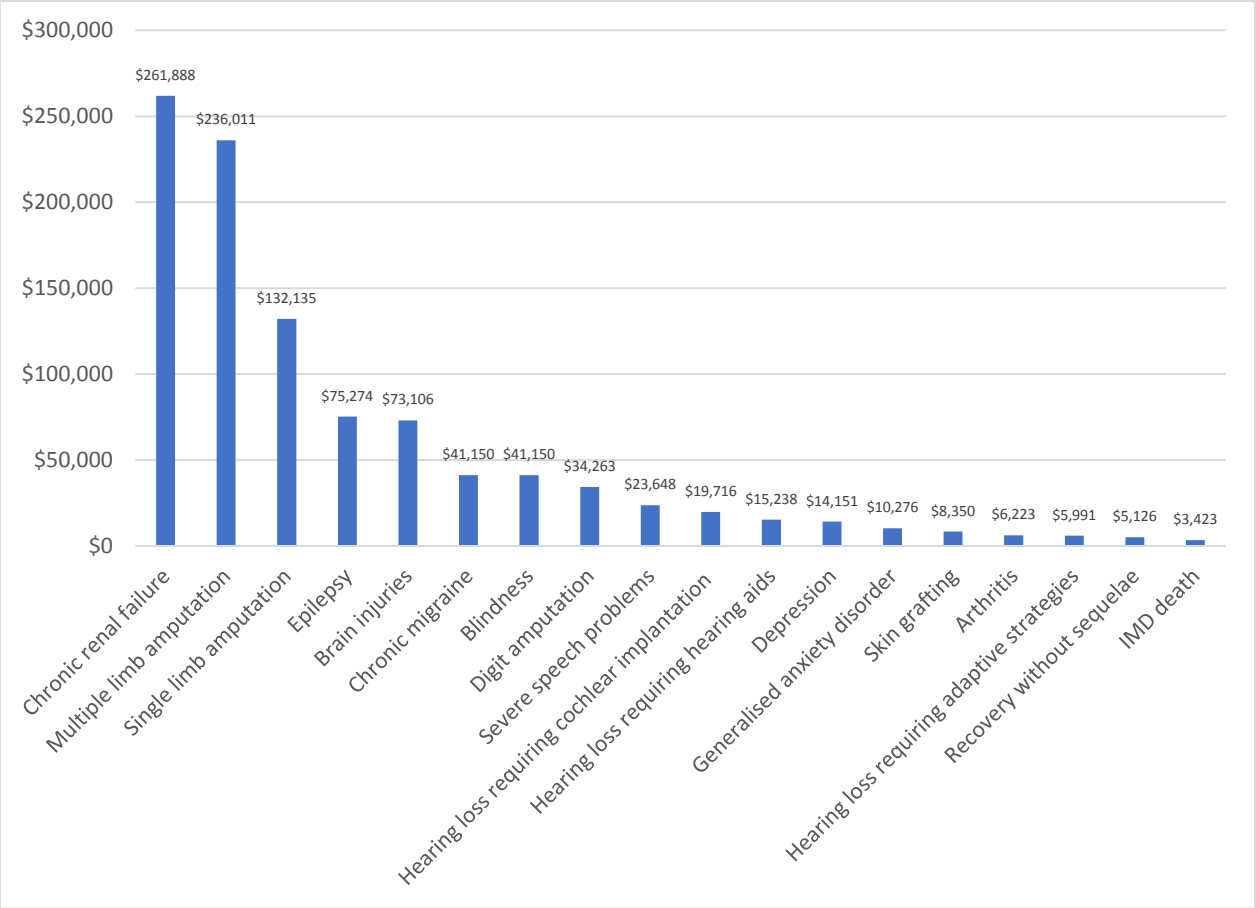
Figure 2 Direct healthcare cost per IMD case by age group



Without discounting, the first-year healthcare cost is around US$20,000 on average (Figure 2). The average long-term healthcare cost is expected to be US$11,787.08 for two-year old children and remains stable for adult patients aged >25 years.

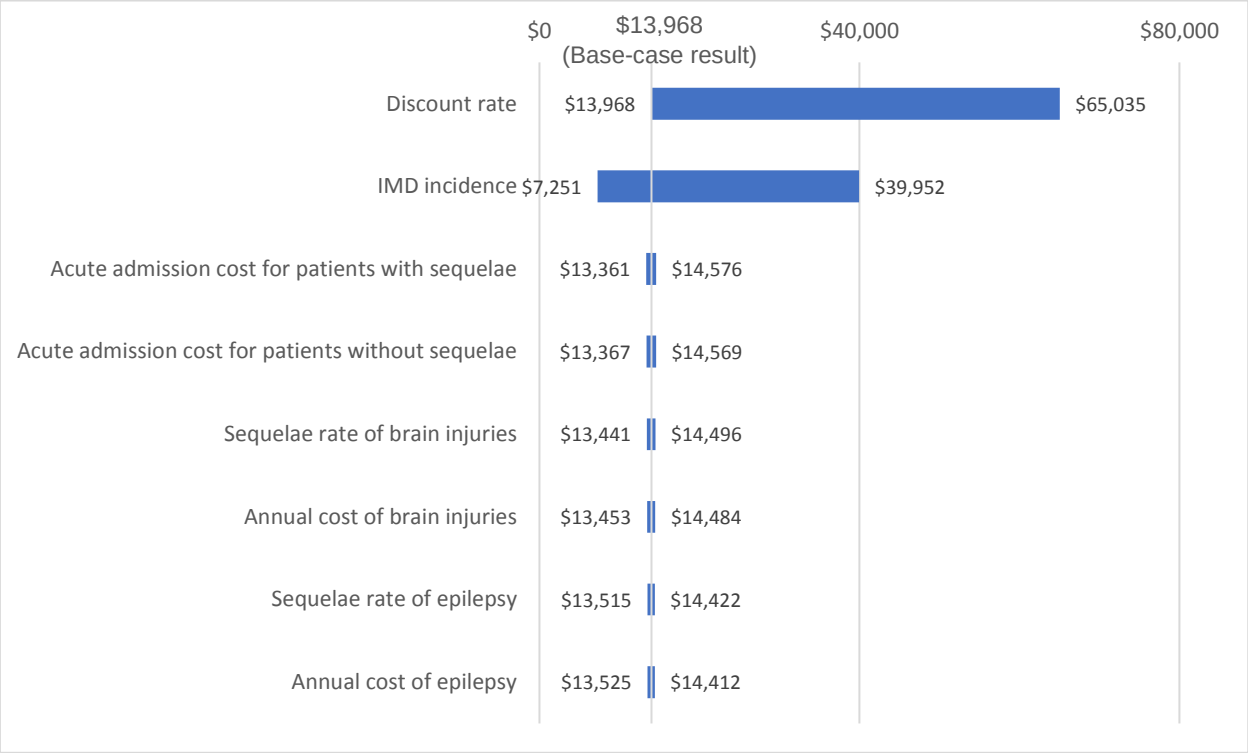
Patients with chronic renal failure, limb amputation, epilepsy and brain injuries are predicted to have higher healthcare costs than other patients (discounted at 5%) (Figure 3).

Figure 3 Direct healthcare cost per IMD case by sequelae type (discounted at 5%)



The discount rate and disease incidence are key drivers of uncertainty in the one-way sensitivity analyses. A tornado diagram presents model inputs with at least 5% impact on the base case result, including the discount rate, disease incidence, acute admission cost, sequelae rate and annual healthcare cost of brain injuries, and sequelae rate and annual healthcare cost of epilepsy (Figure 4). Those parameters modified the cost results by more than 5% and generated the wider uncertainty. The cost result was most strongly affected by discount rates, which produced the largest cost difference of US$51,067.09. The variation in incidence rates also greatly impacted the cost result with a cost difference of US$32,701.70. Other parameters modified the cost result by less than 5% (Supplementary Table 5).

Figure 4 Tornado diagram of the most influential input parameters in the one-way sensitivity analysis



The single birth cohort population shows a steady decline in the model after the cohort reached the age of 50 (Supplementary Figure 3) and presents a similar trend to the Australian population in 2016. Variation in cost results was observed when comparing our results with prior modelling studies.

Discussion

Different from previous modelling studies, quantitative and qualitative research methods were used in our study to develop model structure, potentially improving the accuracy of our model predictions.

In a Canadian cost-effectiveness study, the cumulative direct medical cost would average at C$7,055-8,001 per case discounted at 5% (2014 Canadian dollar) [16]. After adjusting inflation and converting to US dollars, the direct cost per case was only half of our estimates. However, in another Canadian study, the average treatment cost of MenB cases could be around C$27,410 with a discount rate of 5% (2012 Canadian dollar) [26]. In a cost-effectiveness study conducted in the Netherlands, the direct cost per case could be approximately €16,667 (2009 euro) discounted at 4% with a total cost of €0.65 million for 39 cases [21]. A French cost-effectiveness study reported that the cumulative direct healthcare cost could be €600 million (2010 euro) for 52,800 cases which would equal €11,036 per case (discounted at 4% within the first 30 years and 2% thereafter) [20]. Variations in perspectives, model structures, input values and methods may be reasons for differences in costs.

The costs are sensitive to changes in the discount rate. This factor was reported to be most influential parameters in other cost-effectiveness analyses [16,17,20]. The more time that has elapsed between birth and predicted events, the higher the reduction in the current value of costs. How and whether to use discounting is controversial when evaluating vaccine programs with potentially long time lags between the time of vaccination and time of its prevention effects [48,49].

Our study showed the disease incidence is another key driver of differences in costs. The disease incidence is highest in infants, which may partially explain why the infant vaccination was more cost-effective than other strategies without considering carriage reductions and indirect protection [15]. In our study, the highest direct healthcare cost was predicted to be incurred in infants, consistent with the highest disease incidence occurring in this age group. Despite widespread vaccination providing protection against serogroup C disease, there are unpredictable natural fluctuations in the incidence of other serogroup diseases over time. In Australia, the number of IMD notifications declined to 147 in 2013 and rose to 381 in 2017. Although the number of IMD cases might be low over a short period of time, the disease burden should not be underestimated in the long term.

Our model was developed based on a thorough review of clinical and modelling literature and expert engagement. Unlike previous health economic analyses, surgical revision costs were included in our model. Multiple surgical reinterventions after initial amputation are often required to treat bony outgrowth, growth arrest, and skin contracture in young children [50].

Model inputs were collected from the published literature, which may not represent the current treatment guidelines and costs associated with IMD. Limited epidemiological and costing studies exist especially in paediatric population to inform clinical and economic parameters. Several parameter estimates were derived from the adult population which may underestimate the higher disease burden in children. Moreover, in large observational studies, most patients with disabilities were followed for less than five years. Psychological and social behaviour problems associated with the disease and permanent disabilities (e.g. scaring and amputation) could not be fully investigated. The additional

costs resulting from long-term disabilities are highly likely to be underestimated. Owing to difficulties in estimating frequency and combinations of sequelae, we assumed each patient would have one sequela, consistent with other modelling studies. In reality, among patients with sequelae, around one third had multiple sequelae [51]. To minimise this bias, we attempted to include all important sequelae identified in the literature and suggested by experts. However, the costing impact of multiple sequelae might be enormous, which could not be investigated in sensitivity analyses. Overall, the cost results in our study are conservative.

IMD can result in substantial costs to the healthcare system and society especially in young children. The introduction of new meningococcal vaccine programs deserves substantial consideration because of a significant reduction in disease burden in infancy. Further COI and epidemiological studies on long-term disabilities associated with IMD are warranted to improve model accuracy and reduce parameter uncertainty.

Funding

No funding was received for this study.

Potential conflicts of interest

Professor Helen Marshall is an independent investigator on clinical trials of investigational vaccines manufactured by pharmaceutical companies including GlaxoSmithKline, Novavax and Pfizer. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, Pfizer and Novartis Vaccines. There are no other conflicts of interest to declare.

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References

[1] Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics. **2009**; 123(3):e502-9.

[2] Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. **2012**; 11(9):774-83.

[3] Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther. **2013**; 11(6):597-604.

[4] Molinier L, Bauvin E, Combescure C, et al. Methodological considerations in cost of prostate cancer studies: a systematic review. Value Health. **2008**; 11(5):878-85.

[5] Rice D. Cost of illness studies: what is good about them? Inj Prev. **2000**; 6(3):177-9.

[6] Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. **2014**; 20(4):327-37.

[7] Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. Hum Vaccin. **2011**; 7(4):458-65.

[8] Davis KL, Misurski D, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the US. Hum Vaccin. **2011**; 7(1):96-101.

[9] Karve S, Misurski D, Miller J, Davis KL. Costs of sequelae associated with invasive meningococcal disease: Findings from a US managed care population. Health Outcomes Res Med. **2011**; 2(4):e215-e26.

[10] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine. **2014**; 32(37):4791-8.

[11] Scholz S, Koerber F, Meszaros K, Fassbender RM, Ultsch B, Welte RR, et al. The cost-of-illness for invasive meningococcal disease caused by serogroup B Neisseria meningitidis (MenB) in Germany. Vaccine. **2019**; (in press).

[12] Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. Paediatric drugs. **2013**; 15(1):49-58.

[13] Darba J, Kaskens L, Hark M, Wright C. Costs of surviving meningococcal disease in Spain: evaluation for two cases of severe meningitis and septicaemia. Vaccine. **2014**; 32(39):5006-12.

[14] Benard S, Wright C, Voisine J, Olivier CW, Gaudelus J. Lifetime cost of meningococcal disease in France: Scenarios of severe meningitis and septicemia with purpura fulminans. J Infect Public Health. **2016**; 9(3):339-47.

[15] Christensen H, Irving T, Koch J, et al. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero((R)) to reduce meningococcal group B disease in Germany. Vaccine. **2016**; 34(29):3412-9.

[16] De Wals P, Zhou Z. Cost-effectiveness Comparison of Monovalent C Versus Quadrivalent ACWY Meningococcal Conjugate Vaccination in Canada. Pediatr Infect Dis J. **2017**; 36(7):e203-e7.

[17] Delea TE, Weycker D, Atwood M, et al. Cost-effectiveness of alternate strategies for childhood immunization against meningococcal disease with monovalent and quadrivalent conjugate vaccines in Canada. PLoS One. **2017**; 12(5):e0175721.

[18] Gasparini R, Landa P, Amicizia D, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero(R)) against meningococcal B disease: A cost-effectiveness analysis. Hum Vaccin Immunother. **2016**; 12(8):2148-61.

[19] Hepkema H, Pouwels KB, van der Ende A, Westra TA, Postma MJ. Meningococcal serogroup A, C, W(1)(3)(5) and Y conjugated vaccine: a cost-effectiveness analysis in the Netherlands. PLoS One. **2013**; 8(5):e65036.

[20] Lecocq H, Parent du Chatelet I, Taha MK, Levy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine. **2016**; 34(19):2240-50.

[21] Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GP, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: Crucial impact of changes in incidence. Hum Vaccin Immunother. **2013**; 9(5):1129-38.

[22] Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new MenB vaccine (Bexsero) into the Italian routine infant immunisation programme. PLoS One. **2015**; 10(4):e0123383.

[23] De Wals P, Coudeville L, Trottier P, Chevat C, Erickson LJ, Nguyen VH. Vaccinating adolescents against meningococcal disease in Canada: a cost-effectiveness analysis. Vaccine. **2007**; 25(29):5433-40.

[24] Hanquet GC, Agnew E, Trotter, et al. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study. Health Technology Assessment (HTA). 2014;KCE Reports 231.

[25] Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine. **2013**; 31(23):2638-46.

[26] Tu HA, Deeks SL, Morris SK, et al. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. Vaccine. **2014**; 32(42):5436-46.

[27] Afzali HHA, Bojke L, Karnon J. Model Structuring for Economic Evaluations of New Health Technologies. Pharmacoeconomics. **2018**; 36(11):1309-1319.

[28] Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. Value Health. **2012**; 15(6):804-11.

[29] Gottfredsson M, Reynisson IK, Ingvarsson RF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis. **2011**; 53(9):e117-24.

[30] Martinon-Torres F. Deciphering the Burden of Meningococcal Disease: Conventional and Under-recognized Elements. J Adolesc Health. **2016**; 59(2 Suppl):S12-20.

[31] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. **2013**;16(2):231-50.

[32] Caro JJ, Briggs AH, Siebert U, Kuntz KM, Force I-SMGRPT. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health. **2012**; 15(6):796-803.

[33] Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0). Canberra: Australian Government Department of Health and Ageing; 2016. Available from: https://pbac.pbs.gov.au/. Accessed 15 June 2018.

[34] Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP) (indicator). Available from: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart. Accessed 02 July 2018.

[35] Roed C, Omland LH, Engsig FN, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. PLoS One. **2010**; 5(3):e9662.

[36] Kliegman R. Nelson Textbook of Pediatrics: Elsevier/Saunders; **2011**.

[37] Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication--Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry **2010**; 49(10):980-9.

[38] Mensch A, Beck T, Civello D, et al. Applying GRADE Criteria to Clinical Inputs to Cost-Effectiveness Modeling Studies. Pharmacoeconomics. **2018**; 36(8):987-94.

[39] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ (Clinical research ed). **2004**; 328(7454):1490.

[40] Abraham E, Pellicore RJ, Hamilton RC, Hallman BW, Ghosh L. Stump overgrowth in juvenile amputees. J Pediatr Orthop. **1986**; 6(1):66-71.

[41] Klimisch J, Carmichael KD, Muradov P, Evans EB. Prevalence of stump overgrowth in pediatric burn patient amputations. J Pediatr Orthop. **2011**; 31(2):216-9.

[42] Pellicore RJ, Sciora J, Lambert CN, Hamilton R. Incidence of bone overgrowth in juvenile amputee population. Inter-Clinic Information Bulletin. **1974**; 13(5):1-8.

[43] Tooms RE. Acquired Amputations in Children. In: Bowker JH, Michael JW, American Academy of Orthopaedic Surgeons. Atlas of limb prosthetics: surgical, prosthetic, and rehabilitation principles. 2 ed. Mosby Inc, **1992**.

[44] van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis. **2010**; 69 Suppl 1:i89-91.

[45] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; **2015**. 245-50 p.

[46] Kigozi J, Jowett S, Lewis M, Barton P, Coast J. Estimating productivity costs using the friction cost approach in practice: a systematic review. Eur J Health Econ. **2016**; 17(1):31-44.

[47] Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ. **1995**; 14(2):171-89.

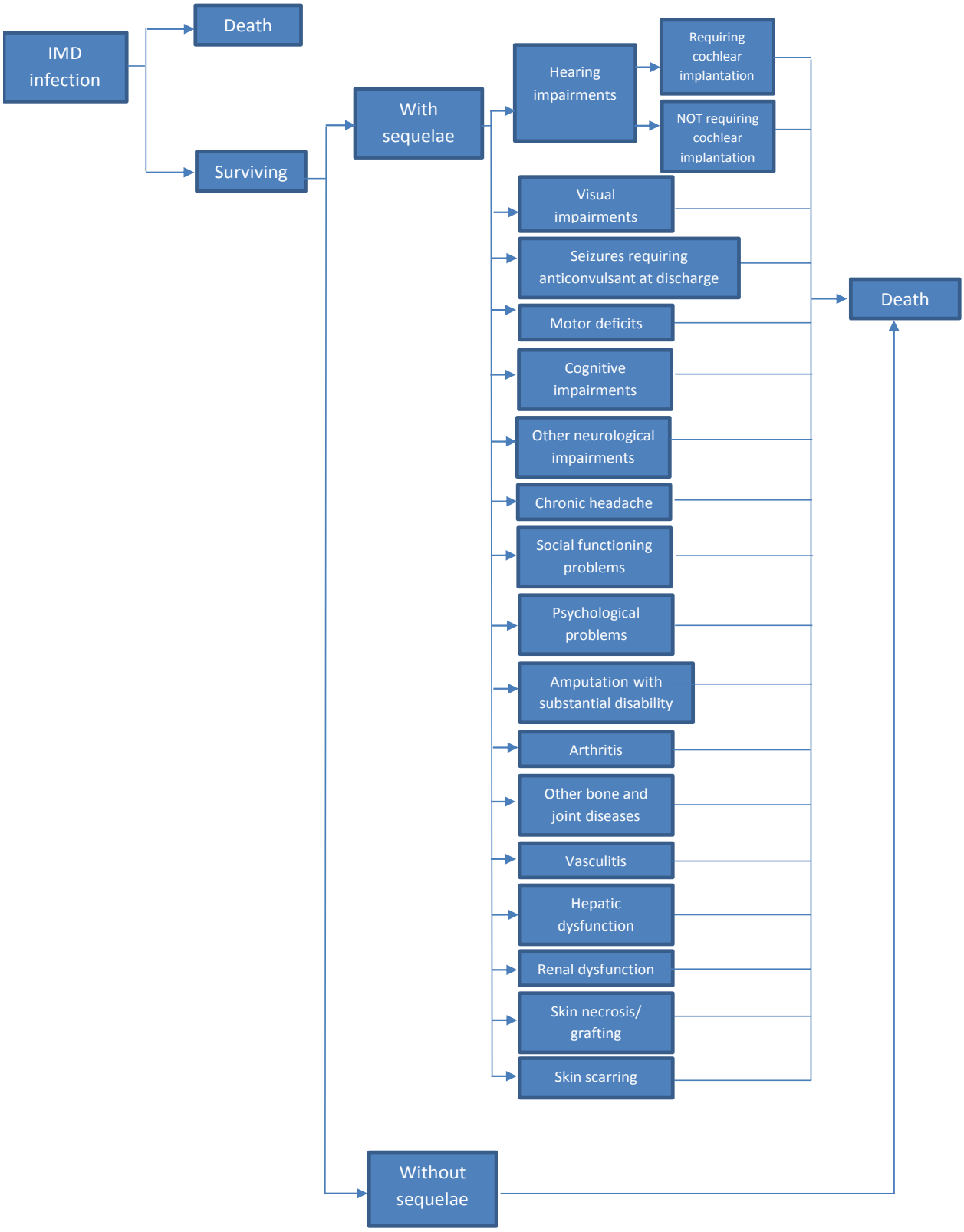
[48] Severens JL, Milne RJ. Discounting health outcomes in economic evaluation: the ongoing debate. Value Health. **2004**; 7(4):397-401.

[49] Jit M, Hutubessy R. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? Appl Health Econ Health Policy. **2016**;14(3):245-52.

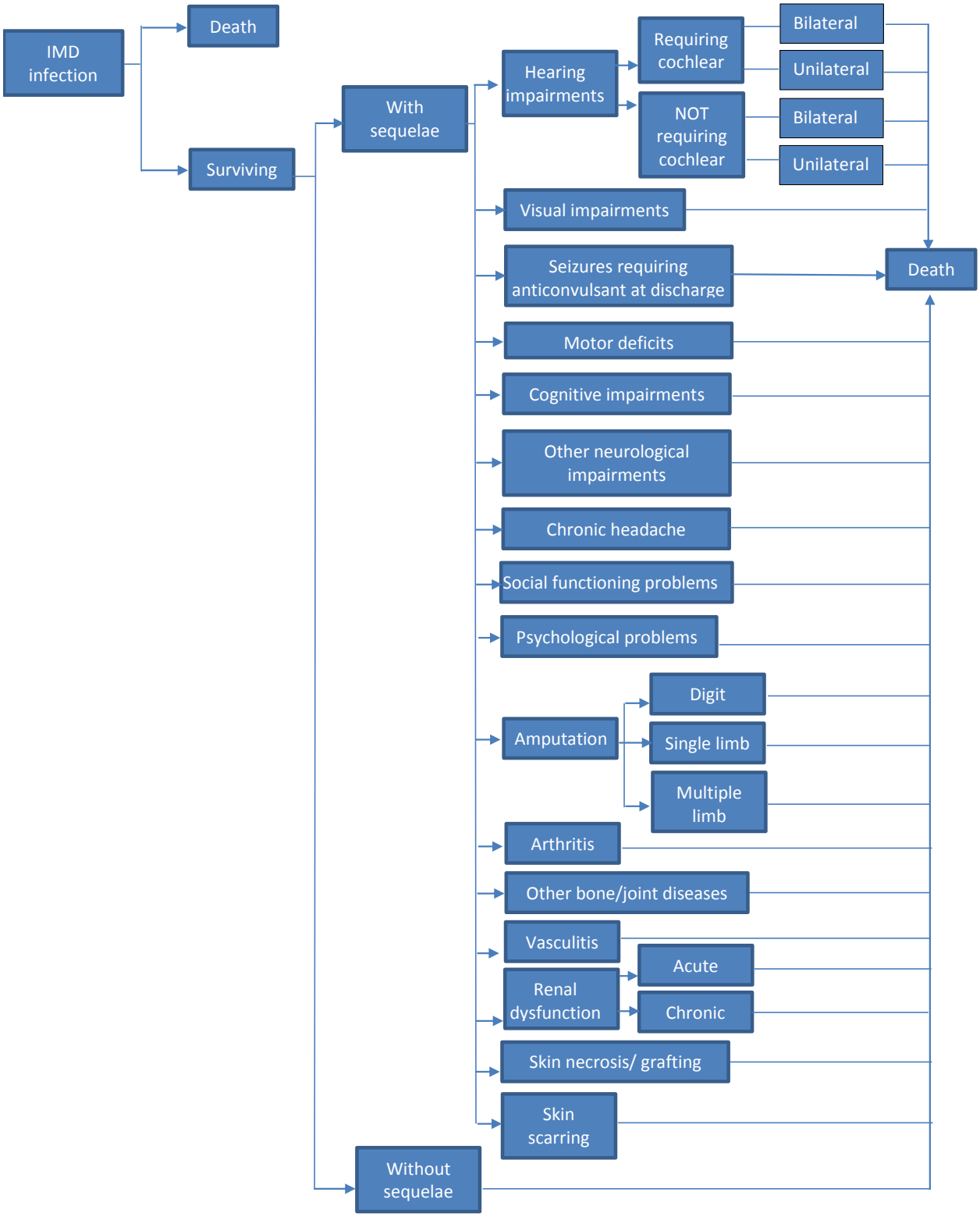
[50] Bache CE, Torode IP. Orthopaedic sequelae of meningococcal septicemia. J Pediatr Orthop. **2006**; 26(1):135-9.

[51] Sadarangani M, Scheifele DW, Halperin SA, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis. **2015**; 60(8):e27-35.

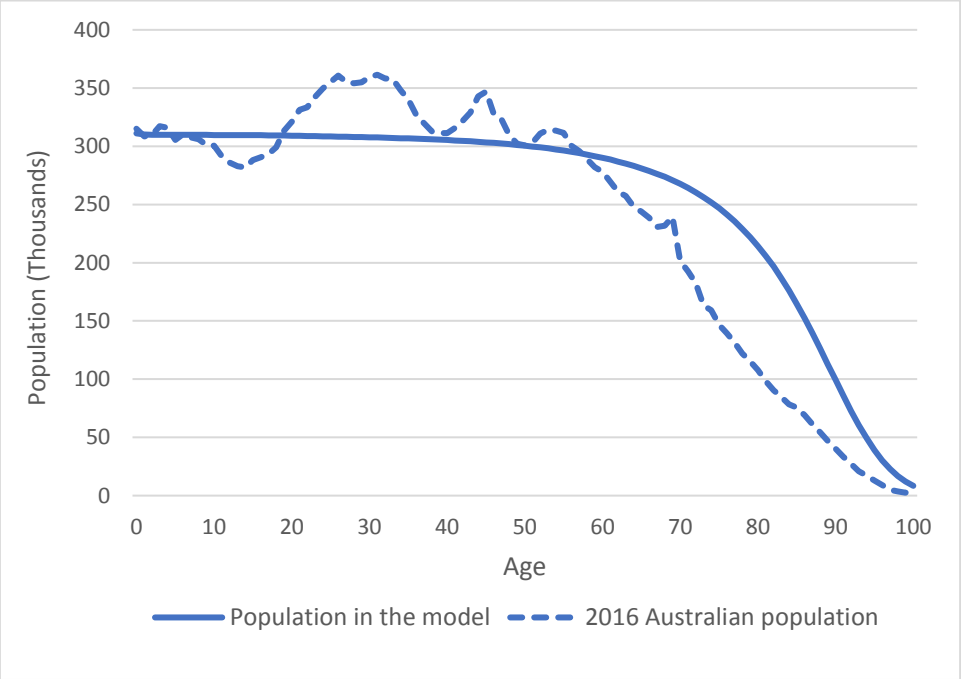
Supplementary Figure 1 Draft conceptual framework



Supplementary Figure 2 Final conceptual framework



Supplementary Figure 3 Comparison of population figures predicted in the Markov model (single birth cohort) and the Australian population in 2016



Supplementary Table 1

IMD Panel Meeting Survey

Name: _____

	Do you think invasive meningococcal disease (IMD) can cause the following sequelae?	**Likelihood of sequelae following IMD** Enter number 1-5: 1 very rare 2 rare 3 uncommon (infrequent) 4 common (frequent) 5 very common	**Impact on life expectancy** Enter number 1-5: *1 very weak 2 weak 3 intermediate 4 strong 5 very strong*	**Impact on resource use** Enter number 1-5: *1 very weak 2 weak 3 intermediate 4 strong 5 very strong*	**Impact on quality of life** Enter number 1-5: *1 very weak 2 weak 3 intermediate 4 strong 5 very strong*
Hearing impairments requiring cochlear implantation	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Hearing impairments Not requiring cochlear implantation	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Visual impairments	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Seizures	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Motor deficits	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Cognitive impairments	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Chronic headache	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Other neurological impairments	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Social functioning	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Psychological problems	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				

	Do you think invasive meningococcal disease (IMD) can cause the following sequelae?	**Likelihood of sequelae following IMD** Enter number 1-5: 1 very rare 2 rare 3 uncommon (infrequent) 4 common (frequent) 5 very common	**Impact on life expectancy** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*	**Impact on resource use** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*	**Impact on quality of life** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*
Amputation	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Arthritis	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Other bone/joint diseases	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Vasculitis	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Hepatic dysfunction	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Renal dysfunction	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Skin necrosis/grating	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				
Skin scarring	No ☐ Yes ☐ If yes, please rate the likelihood and impact.				

	Do you think invasive meningococcal disease (IMD) can cause the following sequelae?	**Likelihood of sequelae following IMD** Enter number 1-5: 1 very rare 2 rare 3 uncommon (infrequent) 4 common (frequent) 5 very common	**Impact on life expectancy** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*	**Impact on resource use** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*	**Impact on quality of life** Enter number 1-5: *1 very weak* *2 weak* *3 intermediate* *4 strong* *5 very strong*
Others: Please specify any other important sequelae, and rate the likelihood and impact. _____ _____ _____ _____ _____ _____					

Supplementary Table 2 Sequelae rates reported in the literature

Supplementary Table 2 Sequelae rates reported in the literature

Paper	Bettinger, 2013	Borg, 2009	Cabellos, 2012	Darton, 2009	Davis, 2011	Fellick, 2001
Study location	Canada	England, UK	Barcelona, Spain	England and Wales, UK	US	Merseyside, UK
Study period	2002-2011	1999-2000	1977-2010	1999-2001	1998-2008	1988-1990
Follow-up period	Up to hospital discharge	18-36 months after disease	FU until the resolution of all symptoms of arthritis	Interviewed 1-3 years after the clinical episode	12 months post 1st admission	8 years following conclusion of recruitment period
Mean/median follow-up time	Mean (95%CI): 24.0 (17.7–30.4) days	Median times from the baseline study interview to the follow-up interview: 583 days (range: 359–1225 days)	Not stated	Not stated	12 Months	Not stated
Study design	Case series	Population-based, matched-cohort	Case series	Case series	Longitudinal retrosepctive	Case-control
Study setting	Active, metropolitan area hospital based surveillance	IMD cases were collected through regional consultants in communicable disease control and clinicians	Health facility	Patient and sepcimen data retrieved from the Meningococcal Reference Unit (MRU) for England and Wales	Patients identified from a health plan claims database	A prospective, multicentre study involving 7 hospitals
Age group	All	15–19 yrs	All	All	All	<16yrs
Clinical diagnosis	Laboratory confirmed MenB	Laboratory confirmed IMD	Laboratory confirmed IMD	Laboratory confirmed IMD	Inpatient admission for IMD with [ICD-9-CM] code 036.x	Labortary confirmed and probable IMD
Sample size	769	101	522	1910 (EDTA samples received by MRU)	173	115
Mean/median age at onset	Median age: 11.9	Mean age at follow-	mean age 30 yrs,	Mean age: 12 yrs	Mean (SD) age:	Median age at diagnosis in months
Control	No	Yes (sequelae only reported in cases)	No	No	No	Yes

Paper	Gottfredsson, 2011 (retrospective cohort study only)	Harrison, 2001	Healy, 2002	Howitz, 2009	Kaplan, 2006	Karve, 2011
Study location	Iceland	Maryland, US	Ireland	Denmark	US	US
Study period	1975-2004	1990-1999	1995-2000	1974–2007	2001-2005	1998-2008
Follow-up period	> 2 weeks after discharge	Not stated	2 months - 5 years	Within 31 days after disease	During or after hospitalisation	12 months post discharge
Mean/median follow-up time	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Study design	Case series	Case series	Case series	Cohort	Case series	Longitudinal retrosepctive cohort
Study setting	Retrospective nationwide study	Population based surveillance study (case report forms completed by hospital infection control staff and supplemented with reviews of medical and health department records)	Retrospective review of IMD cases in children from 2 tertiary referral centers and 2 regional centers in Ireland	The study based on registry data from 4 national registries	Health facilities	Patients identified from an administrative insurance claims database
Age group	All	All	<19yrs	All	≤19yrs	All
Clinical diagnosis	Laboratory confirmed IMD	Laboratory confirmed IMD	Laboratory confirmed IMD	Laboratory confirmed and clinically diagnosed IMD	Laboratory confirmed IMD	Inpatient admission for IMD with [ICD-9-CM] code 036.x
Sample size	541	295 (1992-1999)	407 (serogroup B&C only)	5924 (1974-2007); 2286 (1992-2005)	159	343
Mean/median age at onset	Not stated	For patients	Age by	Median age: 10	Age range: 16	Mean age (SD):
Control	No	No	No	No	No	No

Paper	Maoldomhnaigh, 2016	Nguyen, 2002	Rivero-Calle, 2016	Sadarangani, 2015	Stoof, 2015	Stovall, 2002
Study location	Dublin, Ireland	US	Spain	Canada	Netherlands	Arkansas, US
Study period	2001-2011	1985-1996	2008-2013	2002-2011	1999-2011	1988-2000
Follow-up period	After discharge	Up to hospital discharge	Up to discharge	Up to hospital discharge	At discharge or the year afterward	Up to hospital discharge
Mean/median follow-up time	Not stated	NA	NA	NA	Not stated	Median length of hospital stay: 8 days (range: 2-190 days)
Study design	Case series	Case series	Multicenter retrospective	Prospective cohort study	Case series	Case series
Study setting	Retrospective case review from Dublin's two tertiary referral paediatric hospitals, Our Lady's Children's Hospital and the Children's University Hospital	Children with IMD at 4 paediartic referral hospitals	Retrospective review of all children with IMD to 36 hospitals	Active, prospective, population based surveillance study covering 50% of the Canadian population. Data collected from hospital records	National surveillance based hospital and laboratory data	Retrospective review of medical and microbiologic records from Arkansas Children's Hospital
Age group	≤19 years	<20yrs	<15yrs	All	All	≤21yrs
Clinical diagnosis	Laboratory confirmed IMD	Laboratory confirmed IMD	Laboratory confirmed or probable IMD cases	Laboratory confirmed IMD	Laboratory confirmed IMD	Laboratory confirmed and clinical cases of IMD
Sample size	382	381	458	868	879	150
Mean/median age at onset	Median age was 1.5 years	Mean age in	Median	Children (<18yrs):	Not stated	Median age: 30
Control	No	No	No	No	No	No

Paper	Tsolia, 2009	Viner, 2012	Wang, 2001	Wang, 2014	Point estimates (%)	
Study location	Athens, Greece	England, UK	Boston, US	Adelaide, Australia		
Study period	1999-2003	2004-2006	1981 - 1996	2000-2011		
Follow-up period	Up to discharge	≥3 years after the disease	Up to hospital discharge	After discharge		
Mean/median follow-up time	NA	Median: 3.75 (IQR: 2.86-4.04, range: 2.62-5.61) yrs after disease	Not stated	Mean (95%CI): 645.8 (403.3-939.3) days		
Study design	Case series	Case-control study	Case series	Case series		
Study setting	Children with IMD hospitalised in the area of Athens were prospectively recorded during a 5-year period	Children with IMD recuited from UK National Meningococcal Registry	Retrospective review of medical notes of children with IMD at the 4 paediatric referral hospitals in Boston.	Retrospective review of medical notes of children with IMD admitted to a tertiary paediatric hospital.		
Age group	≤15yrs	≤13yrs	<18yrs	<18yrs		
Clinical diagnosis	Laboratory confirmed IMD	Laboratory confirmed MenB	Laboratory confirmed IMD	Laboratory confirmed and probable IMD cases		
Sample size	262	245	231	109		
Mean/median age at onset	Median age: 51.5	Mean age at follow-up: 6.5 (SD:	Median age	Mean age (SD):		
Control	No	Yes	No	No		

Paper	Bettinger, 2013			Borg, 2009			Cabellos, 2012			Darton, 2009			Davis, 2011			Fellick, 2001			
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	%*
Any seuelae	74	391	18.93%			58.0%				148	504	29.4%		173	41.00%				
Multiple complications	17	391	4.35%																
Hearing problems/impairment						12.0%													
Perceptive hearing loss																			
Sensorineural hearing loss																13	109	11.93%	10.11%
Hearing loss/deficit										65	504	12.90%		173	9.30%	19	109	17.43%	11.98%
→ Bilateral sever to profound sensorineural loss requiring hearing aids																2	109	1.83%	1.83%
→ Unilateral sever to profound sensorineural loss																2	109	1.83%	1.83%
→ Unilateral moderate sensorineural loss																1	109	0.92%	0.92%
→ Unilateral high frequency losses (mild-moderate)																8	109	7.34%	5.52%
→ Conductive hearing loss																6	109	5.50%	1.87%
→ Profound bilateral sensorineural hearing loss (wears cochlear implant or HL≥90db)																			
→ Moderately severe bilateral sensorineural hearing loss (≥40db)																			
→Sensorineural hearing loss (unilateral or bilateral; hearing loss 20-40db)																			
→Any sensorineural hearing loss (unilateral or bilateral; hearing loss≥20db)																			
Deafness	28	391	7.16%																
→ Bilateral deafness																			
→ Unilateral deafness																			
→ Severe bilateral deafness	6	391	1.53%																
→ Severe unilateral deafness	9	391	2.30%																
Blindness	1	391	0.26%											173	1.00%	1	115	0.87%	0.87%
Visual impairment										44	504	8.73%							
Visual disturbance																			
Seizures & Epilepsy																2	115	1.74%	1.74%
Epilepsy															5.80%				
Seizures						2.0%									13.90%				
Seizures requiring anticonvulsant at discharge	10	391	2.56%																
Motor deficits/mobility problems/motor disability	5	391	1.28%			13.0%													
Impaired muscle function																			
Cognitive impairments/dysfunctions	5	391	1.28%													1	115	0.87%	0.87%
Brain injuries	12	391	3.07%																
Brain nerve damage																			
Paresthesia/ reduced sensitivity																			
Tinnitus																			
Speech and communication problems/aphasia						13.0%													
Chronic migraine																			
Any neurologic sequelae (incl developmental dealy, focal neuro deficits, and/or seizures, etc)	12	391	3.07%													2	115	1.74%	1.74%
Other neurological impairments	2	391	0.51%																

Paper	Gottfredsson, 2011			Harrison, 2001			Healy, 2002			Howitz, 2009			Kaplan, 2006			Karve, 2011		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Any seuelae							44	407	10.81%								343	34.10%
Multiple complications																		
Hearing problems/impairment																		
Perceptive hearing loss										44	2286	1.92%						
Sensorineural hearing loss							13	407	3.19%									
Hearing loss/deficit	14	541	2.59%	13	295	4.41%											343	10.50%
→ Bilateral sever to profound sensorineural loss requiring hearing aids																		
→ Unilateral sever to profound sensorineural loss																		
→ Unilateral moderate sensorineural loss																		
→ Unilateral high frequency losses (mild-moderate)																		
→ Conductive hearing loss																		
→ Profound bilateral sensorineural hearing loss (wears cochlear implant or HL≥90db)																		
→ Moderately severe bilateral sensorineural hearing loss (≥40db)																		
→Sensorineural hearing loss (unilateral or bilateral; hearing loss 20-40db)																		
→Any sensorineural hearing loss (unilateral or bilateral; hearing loss≥20db)																		
Deafness													14	159	8.81%			
→ Bilateral deafness													8	159	5.03%			
→ Unilateral deafness													6	159	3.77%			
→ Severe bilateral deafness																		
→ Severe unilateral deafness																		
Blindness																	343	0.90%
Visual impairment																		
Visual disturbance																		
Seizures & Epilepsy	3	541	0.55%															
Epilepsy										33	2367	1.39%					343	7.00%
Seizures													9	159	5.66%		343	11.70%
Seizures requiring anticonvulsant at discharge																		
Motor deficits/mobility problems/motor disability																		
Impaired muscle function																		
Cognitive impairments/dysfunctions	8	541	1.48%															
Brain injuries																		
Brain nerve damage																		
Paresthesia/ reduced sensitivity																		
Tinnitus																		
Speech and communication problems/aphasia																		
Chronic migraine	3	541	0.55%															
Any neurologic sequelae (incl developmental dealy, focal neuro deficits, and/or seizures, etc)							18	407	4.42%									
Other neurological impairments																		

Paper	Maoldomhnaigh, 2016			Nguyen, 2002			Rivero-Calle, 2016			Sadarangani, 2015			Stoof, 2015			Stovall, 2002		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Any seuelae	32	340	9.41%				59	458	12.88%	157	868	18.09%		763	29.00%	18	150	12.00%
Multiple complications										58	868	6.68%						
Hearing problems/impairment																		
Perceptive hearing loss																		
Sensorineural hearing loss	3	340	0.88%													9	150	6.00%
Hearing loss/deficit										46	868	5.30%	43	763	5.64%			
→ Bilateral sever to profound sensorineural loss requiring hearing aids																		
→ Unilateral sever to profound sensorineural loss																		
→ Unilateral moderate sensorineural loss																		
→ Unilateral high frequency losses (mild-moderate)																		
→ Conductive hearing loss																		
→ Profound bilateral sensorineural hearing loss (wears cochlear implant or HL≥90db)																		
→ Moderately severe bilateral sensorineural hearing loss (≥40db)																		
→Sensorineural hearing loss (unilateral or bilateral; hearing loss 20-40db)																		
→Any sensorineural hearing loss (unilateral or bilateral; hearing loss≥20db)																		
Deafness							12	458	2.62%									
→ Bilateral deafness																		
→ Unilateral deafness																		
→ Severe bilateral deafness																		
→ Severe unilateral deafness																		
Blindness																		
Visual impairment													7	763	0.92%			
Visual disturbance										9	868	1.04%						
Seizures & Epilepsy																		
Epilepsy													7	763	0.92%			
Seizures										21	868	2.42%				8	150	5.33%
Seizures requiring anticonvulsant at discharge																		
Motor deficits/mobility problems/motor disability										25	868	2.88%						
Impaired muscle function													33	763	4.33%			
Cognitive impairments/dysfunctions										5	868	0.58%	26	763	3.41%			
Brain injuries																		
Brain nerve damage													9	763	1.18%			
Paresthesia/ reduced sensitivity													4	763	0.52%			
Tinnitus													6	763	0.79%			
Speech and communication problems/aphasia													3	763	0.39%			
Chronic migraine																		
Any neurologic sequelae (incl developmental dealy, focal neuro deficits, and/or seizures, etc)	9	340	2.65%				23	458	5.02%	95	868	10.94%						
Other neurological impairments										16	868	1.84%						

Paper	Tsolia, 2009			Viner, 2012				Wang, 2001			Wang, 2014			Point estimates (%)	
	n	N	%	n	N	%	%*	n	N	%	n	N	%	Min	Max
Any seuelae	31	251	12.35%	87	245	35.51%	20.57%				41	109	37.61%	9.41%	58.00%
Multiple complications														4.35%	6.68%
Hearing problems/impairment											4	109	3.67%	3.67%	12.00%
Perceptive hearing loss														1.92%	1.92%
Sensorineural hearing loss														0.88%	10.11%
Hearing loss/deficit	3	251	1.20%											1.20%	12.90%
→ Bilateral sever to profound sensorineural loss requiring hearing aids														1.83%	1.83%
→ Unilateral sever to profound sensorineural loss														1.83%	1.83%
→ Unilateral moderate sensorineural loss														0.92%	0.92%
→ Unilateral high frequency losses (mild-moderate)														5.52%	5.52%
→ Conductive hearing loss														1.87%	1.87%
→ Profound bilateral sensorineural hearing loss (wears cochlear implant or HL≥90db)				6	245	2.45%	2.45%							2.45%	2.45%
→ Moderately severe bilateral sensorineural hearing loss (≥40db)				5	232	2.16%	1.21%							2.16%	2.16%
→Sensorineural hearing loss (unilateral or bilateral; hearing loss 20-40db)				4	232	1.72%	1.41%							1.72%	1.72%
→Any sensorineural hearing loss (unilateral or bilateral; hearing loss≥20db)				15	232	6.47%	5.21%							6.47%	6.47%
Deafness														2.62%	8.81%
→ Bilateral deafness														5.03%	5.03%
→ Unilateral deafness														3.77%	3.77%
→ Severe bilateral deafness														1.53%	1.53%
→ Severe unilateral deafness														2.30%	2.30%
Blindness				1	239	0.42%	0.42%							0.26%	1.00%
Visual impairment														0.92%	8.73%
Visual disturbance														1.04%	1.04%
Seizures & Epilepsy				5	239	2.09%	1.78%				5	109	4.59%	0.55%	4.59%
Epilepsy														0.92%	7.00%
Seizures														2.00%	13.90%
Seizures requiring anticonvulsant at discharge								4	231	1.73%				1.73%	2.56%
Motor deficits/mobility problems/motor disability											1	109	0.92%	0.92%	13.00%
Impaired muscle function														4.33%	4.33%
Cognitive impairments/dysfunctions														0.58%	3.41%
Brain injuries														3.07%	3.07%
Brain nerve damage														1.18%	1.18%
Paresthesia/ reduced sensitivity														0.52%	0.52%
Tinnitus														0.79%	0.79%
Speech and communication problems/aphasia				10	239	4.18%	3.56%				3	109	2.75%	0.39%	13.00%
Chronic migraine											5	109	4.59%	0.55%	4.59%
Any neurologic sequelae (incl developmental dealy, focal neuro deficits, and/or seizures, etc)	14	251	5.58%								11	109	10.09%	1.74%	10.94%
Other neurological impairments								6	231	2.60%				0.51%	2.60%

%* Minus in control group (numbers not shown here)

FU after discharge

FU until

Supplementary Table 2 Sequelae rates reported in the literature

Paper	Bettinger, 2013	Borg, 2009	Cabellos, 2012	Darton, 2009	Davis, 2011	Fellick, 2001	Gottfredsson, 2011 (retrospective cohort study only)	Harrison, 2001	Healy, 2002	Howitz, 2009	Kaplan, 2006	Karve, 2011	Maoldomhnaigh, 2016	Nguyen, 2002	Rivero-Calle, 2016	Sadarangani, 2015	Stoof, 2015	Stovall, 2002	Tsolia, 2009	Viner, 2012	Wang, 2001	Wang, 2014	Point estimates (%)	
Any psychologic disorder																				61 235 25.96% 15.71%			25.96%	25.96%
Oppostional defiant																				17 149 11.41% 6.15%			11.41%	11.41%
Conduct disorder																				9 149 6.04% 5.60%			6.04%	6.04%
Phobic disorder																				7 149 4.70% 3.39%			4.70%	4.70%
Generalised anxiety disorder																				4 149 2.68% 2.25%			2.68%	2.68%
Separation anxiety disorder																				10 146 6.85% 5.96%			6.85%	6.85%
Depression	1 391 0.26%																						0.26%	0.26%
Amputation	15 391 3.84%	3.0%							1 407 0.25%		2 159 1.26%		6 340 1.76%	17 381 4.46%	10 458 2.18%			7 150 4.67%	2 251 0.80%		7 231 3.03%	2 109 1.83%	0.25%	4.67%
Amputation with sustantial disability																				3 239 1.26% 1.26%			1.26%	1.26%
→ Digital amputation	10 391 2.56%							1 255 0.39%			1 159 0.63%										2 231 0.87%		0.39%	2.56%
→Limb amputation					1.70%							343 2.30%									5 231 2.16%		1.70%	2.30%
→ Single limb amputation	2 391 0.51%							1 255 0.39%															0.39%	0.51%
→ Multiple limb amputation	2 391 0.51%							2 255 0.78%			1 159 0.63%												0.51%	0.78%
Arthritis related to IMD acute infection			39 522 7.47%				31 541 5.73%															7 109 6.42%	5.73%	7.47%
Vasculitis																						1 109 0.92%	0.92%	0.92%
Urinary retention																	2 763 0.26%						0.26%	0.26%
Renal dysfunction	8 391 2.05%														8 458 1.75%	22 868 2.53%							1.75%	2.53%
Renal failure							15 541 2.77%		2 407 0.49%														0.49%	2.77%
→ Acute RF																			7 251 2.79%				2.79%	2.79%
→ Chronic RF					8.70%							343 4.40%							1 251 0.40%				0.40%	8.70%
→ Chronic RF requiring dialysis/renal transplantation	1 391 0.26%																						0.26%	0.26%
Renal insufficiency/ dialysis																	4 763 0.52%						0.52%	0.52%
Adrenal gland insufficiency																	2 763 0.26%						0.26%	0.26%
Deteriorated lung function																	1 763 0.13%						0.13%	0.13%
Skin necrosis/grafting					1.70%							343 2.00%											1.70%	2.00%
Skin necrosis							13 541 2.40%				14 159 8.81%								11 251 4.38%				2.40%	8.81%
Skin graft											4 159 2.52%				12 458 2.62%			8 150 5.33%			5 231 2.16%		2.16%	5.33%
Skin scarring	25 391 6.39%	18.0%							16 407 3.93%				17 340 5.00%			46 868 5.30%	26 763 3.41%						3.41%	18.00%
Scars/ skin lesions, no treatment																	19 763 2.49%						2.49%	2.49%
Scars/ skin lesions requiring treatment																	7 763 0.92%						0.92%	0.92%
Skin necrosis/grafting/scarring																						11 109 10.09%	10.09%	10.09%
Necrosis requiring skin transplantation or																	24 763 3.15%						3.15%	3.15%
Vertigo		17.0%																					17.00%	17.00%
Impairment in upper-limb function		4.0%																					4.00%	4.00%
Symptoms consistent with Raynaud phenomenon		28.0%																					28.00%	28.00%
Limb loss or skin graft				23 504 4.56%																			4.56%	4.56%
Stroke					12.10%							343 14.30%											12.10%	14.30%
Anoxic brain damage					4.10%							343 1.20%											1.20%	4.10%
Quadriparesis					1.70%							343 0.90%											0.90%	1.70%
Obstructive hydrocephalus					1.20%							343 3.20%											1.20%	3.20%
Ataxia					1.00%						4 159 2.52%	343 1.50%					1 763 0.13%						0.13%	2.52%
Learning disabilities/learning-academic difficulties					1.00%	1 115 0.87% 0.87%						343 0.30%											0.30%	1.00%
PTSD																						1 109 0.92%	0.92%	0.92%
Eating disorder																				1 148 0.68% 0.68%			0.68%	0.68%
ADHD						3 115 2.61% 0.79%														17 149 11.41% 9.66%			0.79%	11.41%
Autistic spectrum disorder																				2 149 1.34% 1.34%		1 109 0.92%	0.92%	1.34%
Hemorrhage							13 541 2.40%																2.40%	2.40%
Pericarditis							3 541 0.55%																0.55%	0.55%
Cerebral palsy and plegias										7 2367 0.31%		343 0.30%											0.30%	0.31%
Peripheral paralysis/-esis																	10 763 1.31%						1.31%	1.31%
Hemiplegia											3 159 1.89%												1.89%	1.89%
Mental retardation												343 0.30%					4 763 0.52%						0.30%	0.52%
Unsteady gait/gait disturbance															1 458 0.22%								0.22%	0.22%
Skin lesions (ulcers, cellulitis)															7 458 1.53%								1.53%	1.53%
Mild pulmonary hypertension															2 458 0.44%								0.44%	0.44%
Muscle/tendon injuries															2 458 0.44%								0.44%	0.44%
Venous thrombosis															1 458 0.22%								0.22%	0.22%
Joint problems																11 868 1.27%							1.27%	1.27%
Bone & joint problems																						9 109 8.26%	8.26%	8.26%
Haenatology (anaemia and/or thromobytosis)																	7 763 0.92%					2 109 1.83%	0.92%	1.83%
Fatigue/ deteriorated condition/headeache/ myalgia/ arthralgia																	48 763 6.29%						6.29%	6.29%
Lethargy																						5 109 4.59%	4.59%	4.59%

%* Minus in control group (numbers not shown here)

Supplementary Table 3 Epidemiological/clinical input parameters

Parameter	Base case	Reference/ source
IMD incidence	1.5 per 100,000 population (variable by age)	[1]
Case fatality rate	Results from a systematic review and meta-analysis	
Proportion of patients requiring ambulance transfer (%)	48.0	[2]
Proportion of sequelae (%)		
Hearing loss requiring cochlear implantation	2.45	[3]
Hearing loss requiring hearing aids	2.16	[3]
Hearing loss requiring adaptive listening strategies only	1.72	[3]
Blindness	0.42	[3]
Epilepsy	2.56	[4]
Brain injuries including cognitive impairments	3.07	[4]
Severe speech and communication problems	4.18	[3]
Chronic migraine	0.55	[5]
Generalised anxiety disorder	2.68	[3]

Parameter	Base case	Reference/ source
Depression	0.26	[4]
Digit amputation	2.56	[4]
Single limb amputation	0.51	[4]
Multiple limb amputation	0.51	[4]
Arthritis	7.47	[6]
Chronic renal failure requiring dialysis/renal transplantation	0.26	[4]
Skin grafting	2.62	[7]

Supplementary Table 4 Cost input parameters (US$)

Parameter		Base case	Reference/ source
Direct healthcare costs associated with acute admissions			
Acute admission cost	One-off cost	$12,316.96 (recovery with no sequelae)	National Hospital Data Collection
		$16,859.38 (recovery with sequelae)	National Hospital Data Collection
Follow-up care for patients without sequelae	One-off cost	$58.12	MBS* item 104 [8]
Public health management	One-off cost	$521.10	[9]
Direct healthcare costs associated with sequelae			
Hearing loss requiring cochlear implantation	One-off cost	$40,721.38	[10]
Hearing loss requiring hearing aids	One-off cost	$4,792.08	[10]
	Annual cost	$1,146.66	[10]
Hearing loss requiring adaptive listening strategies	One-off cost	$274.23	[10]
Blindness	Annual cost	$13,958.99 (first year)	[11]

Parameter		Base case	Reference/ source
		$4,777.18 (subsequent years)	[11]
Epilepsy	Annual cost	$10,312.82	[12]
Brain injuries	Annual cost	$31,213.12 (within the first 6 years)	[13]
		$2,366.40 (after first 6 years)	[13]
Severe speech and communication problems	Annual cost	$5,298.90 (within the first 2 years)	Expert opinion
		$2,348.07 (after the first 2 years)	[14]
Chronic migraine	Annual cost	$5,710.41	[15]
Generalised anxiety disorder	Annual cost	$1,971.37	[16]
Depression	Annual cost	$3,934.53	[17]
Digital amputation	One-off cost	$16,253.83	AR-DRG fee
	Annual cost	$3,396.73	Expert opinion
Single limb amputation	One-off cost	$55,767.12 (0-18 years)	[18], AR-DRG fee, expert opinion

Parameter		Base case	Reference/ source
		$63,059.76 (>18 years)	[18], AR-DRG fee, expert opinion
	Annual cost	$19,701.05 (0-18 years)	Expert opinion
		$13,586.93 (>18 years)	Expert opinion
Multiple limb amputation	One-off cost	$69,354.05 (0-18 years)	[18], AR-DRG fee, expert opinion
		$76,646.69 (>18 years)	[18], AR-DRG fee, expert opinion
	Annual cost	$33,287.98 (0-18 years)	Expert opinion
		$27,173.86 (>18 years)	Expert opinion
Stump revision	One-off cost	$36,745.42	AR-DRG fee
Arthritis	One-off cost	$957.86	[19]
Chronic renal failure requiring dialysis/renal transplantation	One-off cost	$40,857.76	[20-22]
	Annual cost	$38,873.59	[20-22]

Parameter		Base case	Reference/ source
Skin necrosis and grafting	One-off cost	$7,227.14	AR-DRG fee
Direct non-healthcare costs			
Ambulance	One-off cost	$2,713.31	South Australia Ambulance Services
Hearing loss requiring cochlear implantation or hearing aids	Annual cost	$12,802.96 (early intervention for children aged <5 years)	[10]
		$30,543.42 (special education)	[10]
		$2,560.43 (informal care)	[10]
Blindness	Annual cost	$20,540.16 (special education)	[23]
		$2,312.19 (informal care, out-of-pocket and other costs)	[24]
Brain injuries	Annual cost	$11475.27 (long term care, equipment and home modification costs within the first 6 years)	[13]

Parameter		Base case	Reference/ source
		$10388.37 (long term care, equipment and home modification costs after first 6 years)	[13]
		$20,540.16 (special education)	[24]
Severe speech and communication problems	Annual cost	$20,540.16 (special education)	[24]
Generalised anxiety disorder	Annual cost	$289.75 (out-of-pocket costs and others)	[16]
Chronic renal failure requiring dialysis/renal transplantation	One-off cost	$1,507.49 (out-of-pocket costs and others)	[20-22]
	Annual cost	$2,095.77 (out-of-pocket costs and others)	[20-22]
Indirect costs (HC method)			
Acute admission	One-off cost	Productivity loss: 6.91 days (recovery without sequelae)	National Hospital Data Collection
		Productivity loss: 11.84 days (recovery with sequelae)	National Hospital Data Collection

Parameter		Base case	Reference/ source
Premature death caused by IMD	Annual cost	Productivity value of life years lost during working age	[25,26]
Hearing loss requiring cochlear implantation or hearing aids	Annual cost	$2,422.55	[10]
Blindness	Annual cost	$5,034.67	[27]
Epilepsy	Annual cost	Productivity loss: 49.0 days	[25,26,28]
Severe speech and communication problems	Annual cost	$34,548.53	[24]
Generalised anxiety disorder	Annual cost	Productivity loss: 38.7 days	[16,25,26]
Chronic Migraine	Annual cost	Productivity loss: 8.99 weeks	[25,26,29]
Limb amputation	Annual cost	$6,699.69	[30]
Chronic renal failure requiring dialysis/renal transplantation	Annual cost	$9,289.85	[31]
Skin necrosis and grafting	One-off cost	Productivity loss: 4 days	National Hospital Data Collection

Parameter		Base case	Reference/ source
Total direct and indirect costs (HC method)			
Brain injuries	Annual cost	$72,348.09	[13]
Depression	Annual cost	$12,690.96	[17]
Indirect costs (FC method)			
Premature death caused by IMD		Productivity loss: 3 months	[25,32]
Brain injuries, chronic renal failure requiring dialysis/renal transplantation or multiple limb amputation		Productivity loss:1.5 months	[25,32]

*MBS = medical benefits schedule (http://www.mbsonline.gov.au)

Supplementary Table 5 Sensitivity analysis results (US$)

	Parameter range	Low value	High value
Discounting rate	0, 3.5%, 5%	$13,968.40	$65,035.49
IMD incidence	Historically low & high records	$7,250.78	$39,952.48
Acute admission cost for patients with sequelae	± 25%	$13,360.87	$14,575.94
Acute admission cost for patients without sequelae	± 25%	$13,367.37	$14,569.44
Sequelae rate of brain injuries	± 25%	$13,441.07	$14,495.74
Annual cost of brain injuries	± 25%	$13,452.75	$14,484.06
Sequelae rate of epilepsy	± 25%	$13,515.01	$14,421.79
Annual cost of epilepsy	± 25%	$13,524.74	$14,412.06
Sequelae rate of multiple limb amputation	± 25%	$13,671.91	$14,264.90
Annual cost of multiple limb amputation	± 25%	$13,813.95	$14,387.22
Sequelae rate of severe speech problems	± 25%	$13,766.81	$14,169.99
Sequelae rate of digit amputation	± 25%	$13,777.27	$14,159.53
Annual cost of severe speech problems	± 25%	$13,782.73	$14,154.08
Annual cost of single limb amputation	± 25%	$13,930.95	$14,270.23

	Parameter range	Low value	High value
Sequelae rate of chronic renal failure	± 25%	$13,803.60	$14,133.21
Sequelae rate of single limb amputation	± 25%	$13,804.87	$14,131.94
Annual cost of chronic renal failure	± 25%	$13,813.44	$14,123.36
Annual cost of digit amputation	± 25%	$13,822.28	$14,114.53
Sequelae rate of hearing loss requiring cochlear implantation	± 25%	$13,874.49	$14,062.32
One-off cost of hearing loss requiring cochlear implantation	± 25%	$13,883.80	$14,053.00
Sequelae rate of depression	± 25%	$13,962.66	$14,113.16
Sequelae rate of hearing loss requiring hearing aids	± 25%	$13,909.89	$14,026.92
Sequelae rate of chronic migraine	± 25%	$13,912.99	$14,023.82
Annual cost of chronic migraine	± 25%	$13,915.10	$14,021.70
Cost of public health management	± 25%	$13,924.20	$14,012.61
Annual cost of hearing loss requiring hearing aids	± 25%	$13,926.85	$14,009.96
Sequelae rate of generalised anxiety disorder	± 25%	$13,926.85	$14,009.96
Sequelae rate of blindness	± 25%	$13,929.97	$14,006.83
Case fatality rates	95% confidence intervals	$13,930.98	$14,005.83

	Parameter range	Low value	High value
Annual cost of generalised anxiety disorder	± 25%	$13,931.28	$14,005.53
One-off cost of digit amputation	± 25%	$13,933.13	$14,003.67
Sequelae rate of arthritis	± 25%	$13,933.91	$14,002.90
Annual cost (after 1st year) of blindness	± 25%	$13,936.51	$14,000.29
One-off cost of multiple amputation	± 25%	$13,935.21	$13,995.46
Sequelae rate of skin necrosis and grafting	± 25%	$13,942.37	$13,994.43
One-off cost of single amputation	± 25%	$13,941.11	$13,989.56
Cost of skin necrosis and grafting	± 25%	$13,952.34	$13,984.47
One-off cost of chronic renal failure	± 25%	$13,958.34	$13,978.47
One-off cost of hearing loss requiring hearing aids	± 25%	$13,959.64	$13,977.16
Sequelae rate of hearing loss requiring adaptive listening strategies	± 25%	$13,961.44	$13,975.36
One-off cost of arthritis	± 25%	$13,962.33	$13,974.47
Annual cost of depression	± 25%	$13,962.99	$13,973.82
Annual cost (1st year) of blindness	± 25%	$13,963.45	$13,973.35
Cost of follow-up visit	± 25%	$13,965.57	$13,971.24
One-off of hearing loss requiring adaptive listening strategies	± 25%	$13,968.00	$13,968.80

References

[1] National Notifiable Diseases Surveillance System. Notification Rate of Meningococcal disease (invasive)*, Australia, 2017 by age group and sex. Department of Health; 2017. Available from: http://www9.health.gov.au/cda/source/rpt_5_sel.cfm. Accessed 28 June 2018.

[2] Christensen H, Irving T, Koch J, et al. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero((R)) to reduce meningococcal group B disease in Germany. Vaccine. **2016**; 34(29):3412-9.

[3] Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. **2012**; 11(9):774-83.

[4] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J. **2013**; 32(1):e20-5.

[5] Gottfredsson M, Reynisson IK, Ingvarsson RF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis. **2011**; 53(9):e117-24.

[6] Cabellos C, Nolla JM, Verdaguer R, et al. Arthritis related to systemic meningococcal disease: 34 years' experience. European Society of Clinical Microbiology. **2012**; 31(10):2661-6.

[7] Rivero-Calle I, Vilanova-Trillo L, Pardo-Seco J, Salvado LB, Quinteiro LI, Martinon-Torres F. The Burden of Pediatric Invasive Meningococcal Disease in Spain (2008-2013). Pediatr Infect Dis J. **2016**; 35(4):407-13.

[8] Gordon LG, Tuffaha HW, James R, et al. Estimating the healthcare costs of treating prostate cancer in Australia: A Markov modelling analysis. Urol Oncol. **2018**; 36(3):91 e7- e15.

[9] Letouze D, Yao G, Clarke SC. The costs associated with the public health management of a cluster of meningococcal infection in England. Vaccine. **2014**; 32(43):5549-51.

[10] Deloitte Access Economics. The Social and Economic Cost of Hearing Loss in Australia – June 2017. 2017. Available from: http://www.hcia.com.au/about-hearing-loss/#.WkVAwGdCcso. Accessed 29 Dec 2017.

[11] Clarke P, Leal J, Kelman C, Smith M, Colagiuri S. Estimating the cost of complications of diabetes in Australia using administrative health-care data. Value Health. **2008**; 11(2):199-206.

[12] Willems LM, Richter S, Watermann N, et al. Trends in resource utilization and prescription of anticonvulsants for patients with active epilepsy in Germany from 2003 to 2013 - A ten-year overview. Epilepsy Behav. **2018**; 83:28-35.

[13] Access Economics. The economic cost of spinal cord injury and traumatic brain injury in Australia. Report by Access Economics for the Victorian Neurotrauma Initiative Canberra: Access Economics. **2009**; 31.

[14] Ellis C, Simpson AN, Bonilha H, Mauldin PD, Simpson KN. The one-year attributable cost of poststroke aphasia. Stroke. **2012**; 43(5):1429-31.

[15] Lanteri-Minet M. Economic burden and costs of chronic migraine. Curr Pain Headache Rep. **2014**; 18(1):385.

[16] Rovira J, Albarracin G, Salvador L, Rejas J, Sánchez-Iriso E, Cabasés JM. The Cost of Generalized Anxiety Disorder in Primary Care Settings: Results of the ANCORA Study. Community Ment Health J. **2012**; 48(3):372-83.

[17] Goldney RD, Fisher LJ, Grande ED, Taylor AW, Hawthorne G. Have education and publicity about depression made a difference? Comparison of prevalence, service use and excess costs in South Australia: 1998 and 2004. Aust N Z J Psychiatry. **2007**; 41(1):38-53.

[18] MacKenzie EJ, Jones AS, Bosse MJ, et al. Health-care costs associated with amputation or reconstruction of a limb-threatening injury. J Bone Joint Surg Am. **2007**; 89(8):1685-92.

[19] Ackerman I, Bohensky M, Pratt C, Gorelik A, Liew D. Counting the Cost Part 1: Healthcare Costs: The Current and Future Burden of Arthritis. Sydney, Australia: Arthritis Australia. 2016.

[20] NSW Health. NSW Dialysis Costing Studies Presentation to CHSD. 2009. Available from: ahsri.uow.edu.au/chsd/content/groups/public/@web/@chsd/.../doc/uow082154.pdf. Accessed 28 June 2018.

[21] Cass A, Chadban S, Gallagher M, et al. The economic impact of end-stage kidney disease in Australia: Projections to 2020. Melbourne: Kidney Health Australia. 2010.

[22] Australia and New Zealand Dialysis and Transplant Registry. 40th Report, Chapter 2: Prevalence of Renal Replacement Therapy for End Stage Kidney Disease. Adelaide, Australia: 2018. Available from: http://www.anzdata.org.au/v1/report_2017.html. Accessed 28 June 2018.

[23] Chou SL, Lamoureux E, Keeffe J. Methods for measuring personal costs associated with vision impairment. Ophthalmic Epidemiol. **2006**; 13(6):355-63.

[24] Gasparini R, Landa P, Amicizia D, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero(R)) against meningococcal B disease: A cost-effectiveness analysis. Hum Vaccin Immunother. **2016**; 12(8):2148-61.

[25] Australian Bureau of Statistics. Data Cube 10. ALL EMPLOYEES, Number of employees, Average weekly total cash earnings–Rate of pay: by Age category. Australian Bureau of Statistics; 2017. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/6306.0May%202016?OpenDocument. Accessed 28 June 2018.

[26] Australian Bureau of Statistics. Table 22. Underutilised persons by Age and Sex - Trend, Seasonally adjusted and Original Australian Bureau of Statistics; 2017. Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/6202.0May%202018?OpenDocument. Accessed 28 June 2018.

[27] Lafuma A, Brezin A, Fagnani F, Mimaud V, Mesbah M, Berdeaux G. Nonmedical economic consequences attributable to visual impairment: a nation-wide approach in France. Eur J Health Econ. **2006**; 7(3):158-64.

[28] Ivanova JI, Birnbaum HG, Kidolezi Y, Qiu Y, Mallett D, Caleo S. Economic burden of epilepsy among the privately insured in the US. Pharmacoeconomics. **2010**; 28(8):675-85.

[29] Munakata J, Hazard E, Serrano D, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache. **2009**; 49(4):498-508.

[30] Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. **2014**; 37(3):651-8.

[31] Julian-Mauro JC, Cuervo J, Rebollo P, Callejo D. Employment status and indirect costs in patients with renal failure: differences between different modalities of renal replacement therapy. Nefrologia. **2013**; 33(3):333-41.

[32] Kigozi J, Jowett S, Lewis M, Barton P, Coast J. Estimating productivity costs using the friction cost approach in practice: a systematic review. Eur J Health Econ. **2016**; 17(1):31-44.

CHAPTER 4: KNOWLEDGE TRANSLATION, GAPS AND FUTURE RESEARCH

Two online surveys have provided a valuable contribution to the literature because understanding drivers for vaccination in adolescent populations is key to designing effective public health programs. Previous work has only focused on particular vaccines rather than the broad approach to adolescent views taken in this PhD project. The survey results can assist in developing new strategies to improve vaccine uptake in adolescents. Although the school-based immunisation programs have been considered as an efficient way of delivering publicly funded vaccines to adolescents [122], stronger preferences were given to vaccines administered at GP clinics than schools. Adolescents showed willingness to have an active role in the vaccine decision-making process. Without active adolescent engagement with vaccination, ensuring that written information about vaccination reaches parents could be challenging [123]. Only 10% of adolescents considered schools as the most important sources of information about immunisation. However, adolescents were less likely to seek information from health professionals but more likely to source information from school networks in comparison with adults. Educating adolescents, but not their parents, may be a novel approach to improve vaccine uptake. Differences in gender and socioeconomic status should be considered when developing school-based educational programs. Convincing the education sector to include the science of vaccination in an already crowded curriculum could be challenging. Effectiveness and feasibility of school vaccination educational programs needs to be further investigated.

The results derived from the IMD systematic review can help researchers and policy makers understand the clinical and financial burden of the disease and inform future cost-

effectiveness analyses. The review has provided precise estimates for CFR by age and serogroup. Accurate and generalisable data for CFR are essential for economic analyses of new vaccine programs and for interpretation of clinical studies and intervention trials aiming to impact on fatality. The review findings have provided concrete evidence to support government policy making and inform cost-effectiveness evaluations for new meningococcal vaccine programs. The results were provided to the Australian Technical Advisory Group on Immunisation and Pharmaceutical Benefits Advisory Committee (PBAC) to inform the government funding decisions for new meningococcal ACWY vaccine programs. Meningococcal ACWY vaccines replaced meningococcal C vaccines on the NIP for infants in July 2018 and will be NIP-funded for adolescents from April 2019. The review results were used to inform the state government funding decision in South Australia to launch a world first meningococcal B (MenB) vaccine program. The new MenB vaccine program commenced in October 2018 in South Australia. Investigating the burden of IMD has not only provided new evidence to cost-effectiveness analyses, but also improved knowledge and understanding of IMD. The systematic review found the clinical and financial burden associated with long-term disabilities caused by IMD has not been well documented. The difficulty in recruitment may limit the ability to conduct prospective follow-up studies. Retrospective case review study design may be a better option. For a study with a large sample size, searching ICD codes without reviewing medical notes may be an efficient way to identify IMD cases and complications/sequelae. However, coding errors could be an issue. In a previous retrospective case review study [96], 23 out of 132 cases who had a hospital separation code A39.0- A39.9, were not eligible after checking their hospital notes [unpublished data].

The IMD costing study provides data for future modelling evaluation including model conceptualisation, data identification and model validation. The Markov model presented

in the thesis is different to previous modelling studies [74,124-134], as the best available evidence was used to input into the model and the most recent modelling guidelines were followed [135-139]. For example, clinical inputs were identified through a systematic review and selected based on the quality of studies. The conceptualisation process of model structures was not described in prior studies. The quantitative or qualitative process of eliciting expert opinions is not often used. Methods for searching and choosing the best evidence were not justified in those studies. It was found that wide-ranging parameter values were extracted from the published literature to populate the models. Without systematic identification and appropriate selection of parameter values, the quality of modelling studies might be compromised. For example, a cost-effectiveness study estimated the sequelae rate in adults at 20% which was extracted from one college study [126]. Only 28 college students infected with IMD were enrolled in this observational study [140]. Studies with small sample sizes might yield low quality results with wide variance [99]. The PBAC recommended to publicly fund MenACWY vaccines in adolescents and infants in Australia. The health economic model, which was presented in the PBAC submission, only included three health states following the meningococcal infection - ‘alive without long-term complications’, ‘alive with long-term complications’ and ‘dead’. Annual costs for IMD cases with long-term sequelae were sourced from a Canadian study estimating healthcare costs for children with medical complexity over a two-year period [141]. Even, the PBAC questioned the relevance of these costing results to the long-term costs of IMD [78]. The IMD costing model developed in this PhD project may provide a framework for selecting health state and incorporating disease surveillance, clinical epidemiology and health economic data in future cost-effectiveness evaluations.

CHAPTER 5: CONCLUSIONS

This thesis comprises two phrases of enquiry into adolescent immunisation: adolescent vaccine attitudes and the burden of IMD. Adolescents preferred vaccination against a life-threatening illness. IMD is a serious vaccine-preventable disease with high mortality and morbidity rates. The MenACWY vaccine has recently been added to the NIP for adolescents due to a rapid increase of MenW cases. MenB vaccines have not been included on the NIP but are publicly funded for adolescents in South Australia. The disease severity influences vaccine acceptance in adolescents. Therefore, those two interrelated areas of research were investigated together in this thesis. The burden of IMD was evaluated as a case study to demonstrate the severity of the disease and significant healthcare and societal costs resulted from IMD.

Research question one: What are adolescent views about immunisation and how do they differ from adult views?

By using three survey questions in regard to vaccine benefits and safety to predict vaccine hesitancy, a higher level of vaccine hesitancy was demonstrated in adolescent than adults. Adolescents were more concerned about vaccine side effects than adults. Unlike adults, adolescents were less likely to consider health professionals as a main source of vaccine information. Although social media is an essential part of adolescent life, adolescents were less likely to choose the media (e.g. internet) as important sources of information, and were more likely to seek information from social networks including families and schools. Adolescents were more likely to prefer a joint decision with parents or by themselves compared with adults. Adolescents showed eagerness to be involved in the vaccine decision-making process.

Research question two: What are adolescent preferences for vaccination programs and what are the most important factors influencing their decisions?

Stronger preferences were observed for vaccination against a life-threatening illness with a lower price, mild but common side effects and delivery via a skin patch. Although school immunisation programs have been implemented for many years, adolescents prefer receiving vaccines at GP clinics. Willingness to pay results were in line with their preferences.

Research question three: What is known about the disease burden and consequences of IMD?

A systematic review and meta-analysis showed the pooled overall CFR was 8.3% with the highest pooled CFR in serogroup W cases. Although, the disease incidence peaks in children aged less than five, the predicted CFR was higher in adolescents compared with young children. The systematic review also found most commonly reported sequelae were arthritis, neurocognitive sequelae, hearing loss, seizures, speech/communication problems, and amputation. The mean costs of acute admission ranged from I$1,629 to I$50,796. Presence of sequelae (complications) was associated with significantly higher hospitalisation costs. The direct and societal costs associated with long-term sequelae are essential component of the financial burden of IMD. However, costing data on long-term follow-up and productivity loss are lacking.

Research question four: What is the mean lifetime cost of IMD per patient taking healthcare system and societal perspectives?

To estimate the lifetime costs of IMD, a cohort-based state-transition model (Markov) was developed using results obtained from the systematic review and best available costing data to populate the model. The undiscounted lifetime societal cost per IMD case is estimated at US$319,897 including the direct healthcare cost of US$65,035. Given a 5% discount rate, the costs are USD$54,279 and USD$13,968 respectively. The sensitivity analysis shows the discount rate and IMD incidence had a significant impact on costing results.

In conclusion, higher vaccine hesitancy and concerns were demonstrated in adolescents, which may be addressed through a school-based educational program. IMD can impose a substantial burden on patients, their families, the healthcare system and society. New meningococcal vaccine programs are being considered or have already been added to adolescent immunisation schedules. Effectively communicating with adolescents and actively engaging them in vaccination may improve vaccine coverage rates in the future.

APPENDIX

IMD SYSTEMATIC REVIEW PROTOCOL

Systematic Literature Review of the Clinical and Economic Burden of IMD

Primary reviewer: Bing Wang (bing.wang@adelaide.edu.au)

Secondary reviewer: Renee Santoreneos (renee.santoreneos@gmail.com)

Review Question and Objectives

This review aims to identify, review and synthesise the evidence on clinical outcomes and economic costs of invasive meningococcal disease.

The primary objective of this review is to describe the clinical and economic burden of meningococcal B infections in adolescents, including incidences, outcomes of the disease and any costs relevant to the disease. Given that there may be limited data in the published literature on meningococcal B infections in adolescent patients, the review will include all meningococcal infections in all age groups; however, information for meningococcal B infections in adolescents will be presented separately whenever possible.

Search Strategy

Databases

The search strategy will include searches of the following electronic databases:

PubMed

Embase

The Cochrane Library, including the following:

The Cochrane Database of Systematic Reviews

The Cochrane Central Register of Controlled Trials

Database of Abstracts of Reviews of Effectiveness

Specific search terms suitable to the individual databases will be developed. These search terms will include combinations of Medical Subject Headings (MeSH)/Emtree and text words contained in the title and abstract. Appendix 1 presents full listings of the search terms.

Health economic databases will be searched, including the following:

Health Economic Evaluation Database (HEED)

Cost-effectiveness Analysis (CEA) Registry

Health Technology Assessment (HTA) database

Paediatric Economic Database Evaluation (PEDE)

Grey literature available online will be searched for relevant abstracts and/or posters from the following organizations:

Meningitis Research Foundation (MRF)

Infectious Diseases Society of America (IDSA)

International Pathogenic Neisseria Conference (IPNC)

European Society for Paediatric Infectious Diseases (ESPID)

International Congress on Infectious Diseases (ICID)

World Society for Pediatric Infectious Diseases (WSPID)

Australian Society for Infectious Diseases (ASID)

Studies published in English will only be considered for inclusion in this review. The reference list of articles will be searched for additional studies.

Keywords

Keywords to be used will be:

Meningococcal, meningococcal meningitis, meningococcal septicaemia, *Neisseria meningitidis*

AND

Burden, costs, cost analysis, fees, hospital charges, economic model, economics, , expenditure, utilisation, case fatality, complications, sequelae, morbidity, mortality, death rates, incidence, survival analysis, health status.

Search Process

The article selection process will occur in the following two phases (Figure 1):

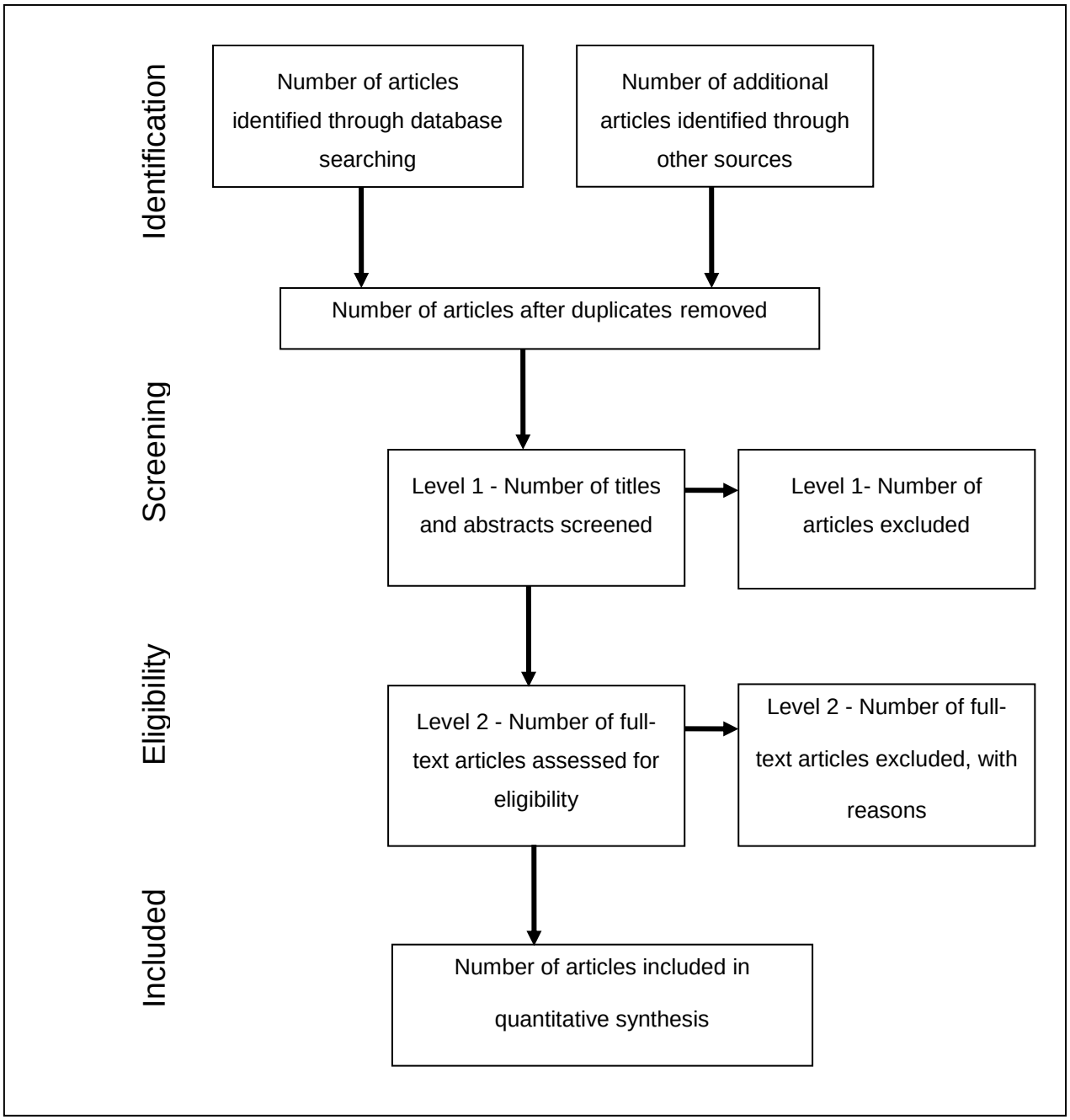
Level 1 screen: Titles and abstracts of articles identified from the electronic databases and from Internet searches will be reviewed.

Level 2 screen: The full text of articles selected at level 1 will be obtained and reviewed for eligibility using the level 2 inclusion and exclusion criteria.

The reference list of all identified reports and articles will also be searched for additional studies.

The inclusion and exclusion processes will be documented, including completion of a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart (Figure 1). This documentation will detail the volume of articles included and excluded at each screening level. The primary reason for exclusion of full text articles will be reported.

Figure 1. PRISMA Diagram for Article Inclusion and Exclusion



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Moher et al., 2009.

Selection Criteria

Table 1 presents the inclusion and exclusion criteria that will be used at the level 1 screening. Table 2 presents the inclusion and exclusion criteria that will be used at the level 2 screening.

Table 1 List of Criteria for the Inclusion and Exclusion of Articles During the Level 1 Screening Process

Criteria	Included	Excluded
Study design	All clinical trials Observational studies International comparisons Health economic studies	Comments and editorials (publication type) Consensus reports Case reports (<10 IMD patients) Qualitative studies Studies in animals but not in humans
Population	Meningococcal infection (age: all)	Studies that include patients with meningococcal infection as part of a larger population but do not present outcomes for the meningococcal infection group separately
Outcomes	No limits[a]	None[a]
Publication date	From 01 January 2000 inclusive	Before 01 January 2000
Language	Studies published in English	

[a] Articles will not be screened on the basis of outcomes at level 1 because all outcomes are often not fully reported in journal abstracts.

Table 2 List of Criteria for the Inclusion and Exclusion of Articles During the Level 2 Screening Process

Criteria	Included	Excluded
Study design	Same as level 1	Same as level 1
Population	Same as level 1	Same as level 1
Outcomes	– Clinical burden o Mortality: case fatality rates only (population based or national surveillance based CFRs; CFRs not grouped by diagnosis or syndrome) o Long-term sequelae (e.g., deafness, neurological deficits, seizures) – Economic burden for acute disease and long-term sequelae o Direct costs for acute disease (e.g., invasive meningococcal disease treatments, containment strategies) o Indirect costs for acute disease (e.g., school days loss, absenteeism for the patient or caregiver)	Studies that do not clearly report any of the included outcomes

Criteria	Included	Excluded
	○ Direct and indirect costs associated with long-term sequelae	

Quality Assessment

The JBI Critical Appraisal Tools will be used to assess case controls, case series, cohort studies, quasi-experimental studies (non-randomised experimental studies), and randomised controlled trials (Appendices 2 – 6).

The quality of the economic or costing studies will be assessed using a checklist (Appendix 7), which was created specifically for this systematic review on the basis of the Drummond 10-point Checklist (Drummond 2015) and ISPOR checklist for retrospective database studies.

Two independent reviewers will assess the quality of studies by using the JBI Critical Appraisal Tools or BMJ Drummond Checklist where appropriate, and any divergences between them will be resolved by discussion.

Data Extraction Methods

Data will be independently extracted by two reviewers using an Excel spreadsheet. The following characteristics of each study will be collected: type of study including study design, multisite or single site and study period, population including sample size and age at illness, country, follow-up duration, perspective, outcome measure, model type (for economic studies only), time horizon (for economic studies only), discount rates (for economic studies only), results, sensitivity analysis (for economic studies only) and funding.

Data Synthesis Methods

Data may be pooled in statistical meta-analysis using STATA software. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated if meta-analysis is performed. Heterogeneity will be assessed statistically using the I^2 statistic and also explored using subgroup analyses based on the different study designs included in this review. PRISMA 2009 checklist will be used for the meta-analysis.

If statistical pooling is not possible due to clinical and methodological heterogeneity, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Appendix 1 Search Terms

PubMed

Invasive Meningococcal Disease	Clinical and Economic Burden	Filters (3221)
meningococcal Infections [mh:noexp] OR Meningitis, Meningococcal [mh:noexp] OR Neisseria meningitidis [mh:noexp] OR Neisseria meningitidis [tiab] OR Meningococc* [tiab]	Case fatality [tiab] OR Complications[tiab] OR Sequela*[tiab] OR Outcome*[tiab] OR Mortality[mh] OR Mortalit*[tiab] OR Death rate* [tiab] OR Incidence*[tiab] OR Morbidity[mh] OR Morbidit*[tiab] OR Health status[mh] OR Health status[tiab] Costs and cost analysis[mh] OR Economics, Medical [mh] OR Fees, Medical[mh] OR Fees, Pharmaceutical[mh] OR Hospital Charges [mh] OR economics[sh] OR	English

	models, economic[mh] OR Economic*[tiab] OR Cost[tiab] OR Costs[tiab] OR Costing*[tiab] OR Burden[tiab] OR Hospitals/utilization[mh] OR Expenditure*[tiab]	

Embase

Invasive Meningococcal Disease	Clinical and Economic Burden (537)	(128)
'Meningococcosis'/syn OR Meningococc*:ab,ti OR 'Neisseria meningitidis'/syn	'Case fatality':ti,ab OR Complication*:ti,ab OR Sequela*:ti,ab OR 'Treatment outcome'/syn OR Outcome*:ti,ab OR 'Mortality'/syn OR Mortalit*:ti,ab OR 'Incidence'/syn OR Incidence:ti,ab OR 'Morbidity'/de OR Morbidity:ti,ab OR	(NOT [medline]/lim) AND [English]/lim

	'Disease course':ti,ab,de OR Burden:ti,ab OR 'Health status':ti,ab,de OR ‘Economic evaluation’/syn Cost*:ab,ti OR Economic* NEAR/5 (illness* OR medical OR model*) OR ‘Health care utilization’/syn OR Utilization:ab,ti OR Utilisation:ab,ti OR Expediture*:ti,ab	

Cochrane

Invasive Meningococcal Disease	Clinical and Economic Burden (220)
MeSH descriptor: [Meningococcal Infections] explode all trees OR MeSH descriptor: [Neisseria meningitidis] explode all trees OR MeSH descriptor: [[Meningitis, Meningococcal]] explode all trees OR Meningococcal:ti,ab,kw (Word variations have been searched)	MeSH descriptor: [Disease Progression] explode all trees OR MeSH descriptor: [Morbidity] explode all trees OR MeSH descriptor: [Treatment Outcome] explode all trees OR MeSH descriptor: [Mortality] explode all trees OR

	“case fatality” OR “morbidity” OR “incidence” OR “sequelae” OR “clinical course " OR “complication*” OR “neurological” OR “deafness” or “seizure*” OR “outcome*”:ti,ab,kw (Word variations have been searched) MeSH descriptor: [Costs and Cost Analysis] explode all trees OR MeSH descriptor: [Models, Economic] explode all trees OR MeSH descriptor: [Economics, Hospital] explode all trees OR MeSH descriptor: [Economics, Medical] explode all trees OR MeSH descriptor: [Economics, Nursing] explode all trees OR MeSH descriptor: [Fees and Charges] explode all trees OR MeSH descriptor: [Health Resources] explode all trees and with qualifier(s): [Utilization - UT] OR “cost*” or “economic*” or "resource use" or "resource utilization" or "resource utilisation" or "direct and indirect cost":ti,ab,kw (Word variations have been searched)

Appendix 2 The JBI Checklist for Case Control Studies

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 3 The JBI Checklist for Case Series

	Yes	No	Unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
3. Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
4. Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
5. Did the case series have complete inclusion of participants?	☐	☐	☐	☐
6. Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
7. Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
8. Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
10. Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 4 The JBI Checklist for Cohort Studies

	Yes	No	Unclear	Not applicable
1. Were the groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to belong enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow-up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 5 The JBI Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4. Was there a control group?	☐	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	☐	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	☐	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 6 The JBI Checklist for Randomized Controlled Trials

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	☐	☐
3. Were treatment groups similar at the baseline?	☐	☐	☐	☐
4. Were participants blind to treatment assignment?	☐	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7. Were treatments groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8. Was follow-up complete, and if not, were strategies to address incomplete follow-up	☐	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	☐	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11. Were outcomes measured in a reliable way?	☐	☐	☐	☐
12. Was appropriate statistical analysis used?	☐	☐	☐	☐
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 7 The Critical Appraisal Checklist for Economic or Costing Studies

	Critical Appraisal Criterion	(Y, N, Not Applicable, Unclear)
Objective	Was (were) the objective(s) and research question(s) of the study described clearly?	
Time horizon	Did the study examine costs or utilisation of the services over an appropriate time horizon?	
Perspective	Was a perspective for the analysis stated?	
Costs & resource utilisation	Were all the important and relevant costs identified?	
	Did it cover all relevant perspective? (Possible perspectives include those of patients and third-party payers; other perspectives may also be relevant depending on the particular analysis.)	
	Were costs measured accurately in appropriate physical units prior to valuation (e.g. hours of nursing time, number of physician visits, lost work-days)?	
	Were the costs generated by the disease of interest or incremental costs (using a disease-free population as a comparison) calculated?	
	If data were collected from or estimated for a period longer than one year, were costs adjusted for differential timing? Was the inflation rate/discount rate mentioned?	
	Was the method of cost calculation clearly documented?	
	Were all costs were valued at the price level of a stated base year?	
	Was the currency in which the costs were calculated reported?	
Data source	Have the data attributes been described in sufficient details to determine whether there was a good rationale for using the data source, the data source's overall generalizability, and how the findings can be interpreted in the context of their own organisation?	
	Have the reliability and validity of the data been described, including any data quality checks and data cleaning procedures?	
	Have the necessary linkages among data sources and/or different care sites been carried out appropriately, taking into account differences in coding and reporting across sources?	
Study population	Have the inclusion and exclusion criteria and the steps used to derive the final sample from the initial population been described? (At least the objective diagnostic criteria (e.g., ICD code and DSM-IV) used to identify eligible patients were reported.)	
	Was the study population clearly defined, including the source of patient recruitment and the	

	Critical Appraisal Criterion	(Y, N, Not Applicable, Unclear)
	sociodemographic and disease characteristics, so as to facilitate the comparison among studies?	
	Has the study included a control group in order to calculate excess costs or, if no control group was involved, were the costs due to the disease of interest (e.g., by diagnostic codes)?	
	If comparison groups were used: a) were they matched, at least in terms of age and/or gender, to allow a direct comparison between equally dispersed groups with regard to their characteristics? or b) was regression analysis carried out in order to control for differences?	
Statistics	What methods have been used to control for other variables that may affect the outcome of interest?	
	Have the authors explained the rationale for the model/statistical method used?	
	Have the authors examined the sensitivity of the results to influential cases? (For example, an individual who is depressed and attempts to commit suicide might have extremely high medical costs that could dramatically change conclusions about the costs of treating a patient with a particular antidepressant therapy. Such “outliers” can be particularly problematic if the sample is small.)	
	Have the authors identified all variables hypothesized to influence the outcome of interest and included all available variables in their model?	
Uncertainty	If a sensitivity analysis was employed, was justification provided for the form(s) of sensitivity analysis employed and the ranges or distributions of values (for key study parameters)?	
	Was heterogeneity in the patient population recognised, for example by presenting study results for relevant subgroups?	
Discussion	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	
	Did the study discuss the generalisability of the results to tother settings and patient groups?	
	Were limitations regarding the calculation of costs and the representativeness of the study population, in particular, discussed in detail?	

REFERENCES (Except for Chapters 2.2.2, 2.3.2, 3.1.1.2, 3.1.3.2, 3.1.4.2, and 3.2.2)

All other references included as component of publications

[1] Principi N, Esposito S. Adolescents and vaccines in the western world. Vaccine. 2013;31(46):5366-74.

[2] Schneyer RJ, Yang C, Bocchini JA, Jr. Immunizing adolescents: a selected review of recent literature and US recommendations. Curr Opin Pediatr. 2015;27(3):405-17.

[3] Gowda C, Schaffer SE, Dombkowski KJ, Dempsey AF. Understanding attitudes toward adolescent vaccination and the decision-making dynamic among adolescents, parents and providers. BMC Public Health. 2012;12:509.

[4] Bernstein HH, Bocchini JA, Jr., Committee On Infectious D. The Need to Optimize Adolescent Immunization. Pediatrics. 2017;139(3).

[5] Kelley AE, Schochet T, Landry CF. Risk taking and novelty seeking in adolescence: introduction to part I. Ann N Y Acad Sci. 2004;1021:27-32.

[6] Balemans R, Devroey D, Van De Vijver E, Chovanova H, Vandevoorde J. Knowledge and attitudes about vaccinations among adolescents. J Prev Med Hyg. 2011;52(2):64-72.

[7] Brown DS, Poulos C, Johnson FR, Chamiec-Case L, Messonnier ML. Adolescent girls' preferences for HPV vaccines: a discrete choice experiment. Adv Health Econ Health Serv Res. 2014;24:93-121

[8] Hessel L. Adolescent and vaccination: knowledge and perception. VHPB, Ljubljana, Slovenia. 2007.

[9] Marshall HS, Chen G, Clarke M, Ratcliffe J. Adolescent, parent and societal preferences and willingness to pay for meningococcal B vaccine: A Discrete Choice Experiment. Vaccine. 2016;34(5):671-7.

[10] Marshall HS, Proeve C, Collins J, Tooher R, O'Keefe M, Burgess T, et al. Eliciting youth and adult recommendations through citizens' juries to improve school based adolescent immunisation programs. Vaccine. 2014;32(21):2434-40.

[11] Pelucchi C, Esposito S, Galeone C, Semino M, Sabatini C, Picciolli I, et al. Knowledge of human papillomavirus infection and its prevention among adolescents and parents in the greater Milan area, Northern Italy. BMC Public Health. 2010;10:378.

[12] Wang B, Clarke M, Afzali HH, Marshall H. Community, parental and adolescent awareness and knowledge of meningococcal disease. Vaccine. 2014;32(18):2042-9.

[13] Parrella A, Braunack-Mayer A, Collins J, Clarke M, Tooher R, Ratcliffe J, et al. Prioritizing government funding of adolescent vaccinations: recommendations from young people on a citizens' jury. Vaccine. 2016;34(31):3592-7.

[14] Carolan K, Verran J, Crossley M, Redfern J, Whitton N, Amos M. Impact of educational interventions on adolescent attitudes and knowledge regarding vaccination: A pilot study. PLoS One. 2018;13(1):e0190984.

[15] Sadique MZ, Devlin N, Edmunds WJ, Parkin D. The effect of perceived risks on the demand for vaccination: results from a discrete choice experiment. PLoS One. 2013;8(2):e54149.

[16] Luyten J, Kessels R, Goos P, Beutels P. Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment. Value Health. 2015;18(2):224-33.

[17] Zimet GD, Mays RM, Sturm LA, Ravert AA, Perkins SM, Juliar BE. Parental attitudes about sexually transmitted infection vaccination for their adolescent children. Arch Pediatr Adolesc Med. 2005;159(2):132-7.

[18] Martinon-Torres F. Deciphering the Burden of Meningococcal Disease: Conventional and Under-recognized Elements. J Adolesc Health. 2016;59(2 Suppl):S12-20.

[19] Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther. 2013;11(6):597-604.

[20] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(12):853-61.

[21] Martin NV, Ong KS, Howden BP, Lahra MM, Lambert SB, Beard FH, et al. Rise in invasive serogroup W meningococcal disease in Australia 2013-2015. Commun Dis Intell Q Rep. 2016;40(4):E454-E9.

[22] Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics. 2009;123(3):e502-9.

[23] Caugant DA. Genetics and evolution of Neisseria meningitidis: importance for the epidemiology of meningococcal disease. Infect Genet Evol. 2008;8(5):558-65.

[24] Kliegman RM, Stanton B, Geme JWS, Schor NF, Behrman RE. Nelson Textbook of Pediatrics: Elsevier; 2016.

[25] National Centre for Immunisation Research and Surveillance. Meningococcal vaccines. 2018 [cited 24 Oct 2018]. Available from: http://www.ncirs.edu.au/provider-resources/ncirs-fact-sheets/.

[26] World Health Organization. Health for the world's adolescents: a second chance in the second decade: summary. World Health Organization, 2014.

[27] Gavi. Value of vaccination. 2018 [cited 4 Oct 2018]. Available from: https://www.gavi.org/about/value/.

[28] National Centre for Immunisation Research and Surveillance. Significant events in immunisation policy and practice in Australia. 2018 [cited 4 Oct 2018]. Available from: http://www.ncirs.edu.au/provider-resources/vaccination-history/.

[29] Department of Health. National Immunisation Strategy for Australia, 2013-2018.2013.

[30] Australian Meningococcal Surveillance P. Annual report of the Australian Meningococcal Surveillance Programme, 2002. Commun Dis Intell Q Rep. 2003;27(2):196-208.

[31] Australian Government Department of Health. Invasive Meningococcal Disease National Surveillance Report - With a focus on MenW - 31 March 2018. Canberra: 2018 [updated 06 August 2018; cited 4 November 2018]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/31-Mar18-IMD-Surveillance-report.pdf.

[32] Australian Government Department of Health. National Immunisation Program Schedule. Canberra: 2018 [updated 06 August 2018; cited 19 September 2018]. Available from: https://beta.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule.

[33] World Health Organization. Tracking the New Vaccine Pipeline. 2018 [cited 4 Oct 2018]. Available from: http://www.who.int/immunization/research/clinicaltrials_newvaccinepipeline/en/.

[34] Minister for Health GHM, Liberal Party of Australia,. $52 million to deliver free meningococcal vaccine to teenagers. Somerville, Victoria2018 [updated 25 September 2018; cited 2 October 2018]. Available from: http://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2018-hunt128.htm.

[35] South Australian Meningococcal B Expert Working Group. Meningococcal B Program for South Australia. Adelaide: 2018 [cited 19 September 2018]. Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/about+us/reviews+and+consultation/meningococcal+b+program+for+south+australia.

[36] Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine (4CmenB); 0.5 mL suspension for injection pre-filled syringe; Bexsero® - July 2015.: Pharmaceutical Benefits Scheme; 2015 [cited 15 June 2018]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-07/mulit-component-meningococcal-group-b-vaccine-psd-july-2015.

[37] Hendry AJ. Australian childhood immunisation coverage, 1 July 2015 and 30 June 2016 cohort, assessed as at 30 September 2016. Commun Dis Intell Q Rep. 2017;41(1):E106-e8.

[38] Feldstein LR, Mariat S, Gacic-Dobo M, Diallo MS, Conklin LM, Wallace AS. Global Routine Vaccination Coverage, 2016. MMWR Morb Mortal Wkly Rep. 2017;66(45):1252-5.

[39] National HPV Vaccination Program Register. National (Australia) HPV 3 dose vaccination coverage for adolescents turning 15 years of age. 2018 [cited 4 Oct 2018]. Available from: http://www.hpvregister.org.au/research/coverage-data.

[40] Hull BP, Hendry AJ, Dey A, Beard FH, Brotherton JM, McIntyre PB. Immunisation coverage annual report, 2014. Commun Dis Intell Q Rep. 2017;41(1):E68-E90.

[41] Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. Clin Ther. 2010;32(8):1448-67.

[42] Walker TY, Elam-Evans LD, Yankey D, Markowitz LE, Williams CL, Mbaeyi SA, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2017. MMWR Morb Mortal Wkly Rep. 2018;67(33):909-17.

[43] Public Health England. Annual HPV vaccine coverage 2016 to 2017: by local authority, local team and area team. London: Public Health England; 2018 [cited 4 Oct

2018]. Available from: https://www.gov.uk/government/statistics/annual-hpv-vaccine-coverage-2016-to-2017-by-local-authority-local-team-and-area-team.

[44] Rand CM, Humiston SG, Schaffer SJ, Albertin CS, Shone LP, Blumkin AK, et al. Parent and adolescent perspectives about adolescent vaccine delivery: practical considerations for vaccine communication. Vaccine. 2011;29(44):7651-8.

[45] Dorell C, Yankey D, Kennedy A, Stokley S. Factors that influence parental vaccination decisions for adolescents, 13 to 17 years old: National Immunization Survey-Teen, 2010. Clin Pediatr (Phila). 2013;52(2):162-70.

[46] Rand CM, Schaffer SJ, Humiston SG, Albertin CS, Shone LP, Heintz EV, et al. Patient-provider communication and human papillomavirus vaccine acceptance. Clin Pediatr (Phila). 2011;50(2):106-13.

[47] Bedford H, Lansley M. More vaccines for children? Parents' views. Vaccine. 2007;25(45):7818-23.

[48] Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991-2001. Vaccine. 2005;23(48-49):5670-87.

[49] Casiday R, Cresswell T, Wilson D, Panter-Brick C. A survey of UK parental attitudes to the MMR vaccine and trust in medical authority. Vaccine. 2006;24(2):177-84.

[50] Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. Pediatrics. 2011;127 Suppl 1:S92-9.

[51] Marshall H, Ryan P, Roberton D. Uptake of varicella vaccine--a cross sectional survey of parental attitudes to nationally recommended but unfunded varicella immunisation. Vaccine. 2005;23(46-47):5389-97.

[52] Peretti-Watel P, Raude J, Sagaon-Teyssier L, Constant A, Verger P, Beck F. Attitudes toward vaccination and the H1N1 vaccine: poor people's unfounded fears or legitimate concerns of the elite? Soc Sci Med. 2014;109:10-8.

[53] Zimet GD, Perkins SM, Sturm LA, Bair RM, Juliar BE, Mays RM. Predictors of STI vaccine acceptability among parents and their adolescent children. J Adolesc Health. 2005;37(3):179-86.

[54] Rosenthal SL, Kottenhahn RK, Biro FM, Succop PA. Hepatitis B vaccine acceptance among adolescents and their parents. J Adolesc Health. 1995;17(4):248-54.

[55] Kester LM, Zimet GD, Fortenberry JD, Kahn JA, Shew ML. A national study of HPV vaccination of adolescent girls: rates, predictors, and reasons for non-vaccination. Matern Child Health J. 2013;17(5):879-85.

[56] Arbiol J, Yabe M, Nomura H, Borja M, Gloriani N, Yoshida S. Using discrete choice modeling to evaluate the preferences and willingness to pay for leptospirosis vaccine. Hum Vaccin Immunother. 2015;11(4):1046-56.

[57] Poulos C, Reed Johnson F, Krishnarajah G, Anonychuk A, Misurski D. Pediatricians' preferences for infant meningococcal vaccination. Value Health. 2015;18(1):67-77.

[58] Poulos C, Yang JC, Levin C, Van Minh H, Giang KB, Nguyen D. Mothers' preferences and willingness to pay for HPV vaccines in Vinh Long Province, Vietnam. Soc Sci Med. 2011;73(2):226-34.

[59] Determann D, Korfage IJ, Lambooij MS, Bliemer M, Richardus JH, Steyerberg EW, et al. Acceptance of vaccinations in pandemic outbreaks: a discrete choice experiment. PLoS One. 2014;9(7):e102505.

[60] Ngorsuraches S, Nawanukool K, Petcharamanee K, Poopantrakool U. Parents' preferences and willingness-to-pay for human papilloma virus vaccines in Thailand. J Pharm Policy Pract. 2015;8(1):20.

[61] Gidengil C, Lieu TA, Payne K, Rusinak D, Messonnier M, Prosser LA. Parental and societal values for the risks and benefits of childhood combination vaccines. Vaccine. 2012;30(23):3445-52.

[62] Hofman R, de Bekker-Grob EW, Raat H, Helmerhorst TJ, van Ballegooijen M, Korfage IJ. Parents' preferences for vaccinating daughters against human papillomavirus in the Netherlands: a discrete choice experiment. BMC Public Health. 2014;14:454.

[63] Hofman R, de Bekker-Grob EW, Richardus JH, de Koning HJ, van Ballegooijen M, Korfage IJ. Have preferences of girls changed almost 3 years after the much debated start of the HPV vaccination program in The Netherlands? A discrete choice experiment. PloS One. 2014;9(8):e104772.

[64] de Bekker-Grob EW, Hofman R, Donkers B, van Ballegooijen M, Helmerhorst TJ, Raat H, et al. Girls' preferences for HPV vaccination: a discrete choice experiment. Vaccine. 2010;28(41):6692-7.

[65] Veldwijk J, Lambooij MS, Bruijning-Verhagen PC, Smit HA, de Wit GA. Parental preferences for rotavirus vaccination in young children: a discrete choice experiment. Vaccine. 2014;32(47):6277-83.

[66] Hall J, Kenny P, King M, Louviere J, Viney R, Yeoh A. Using stated preference discrete choice modelling to evaluate the introduction of varicella vaccination. Health Econ. 2002;11(5):457-65.

[67] Veldwijk J, van der Heide I, Rademakers J, Schuit AJ, de Wit GA, Uiters E, et al. Preferences for Vaccination: Does Health Literacy Make a Difference? Med Decis Making. 2015;35(8):948-58.

[68] Cameron MP, Newman PA, Roungprakhon S, Scarpa R. The marginal willingness-to-pay for attributes of a hypothetical HIV vaccine. Vaccine. 2013;31(36):3712-7.

[69] Bishai D, Brice R, Girod I, Saleh A, Ehreth J. Conjoint analysis of French and German parents' willingness to pay for meningococcal vaccine. Pharmacoeconomics. 2007;25(2):143-54.

[70] Flood EM, Ryan KJ, Rousculp MD, Beusterien KM, Divino VM, Block SL, et al. Parent preferences for pediatric influenza vaccine attributes. Clin Pediatr (Phila). 2011;50(4):338-47.

[71] Stockwell MS, Rosenthal SL, Sturm LA, Mays RM, Bair RM, Zimet GD. The effects of vaccine characteristics on adult women's attitudes about vaccination: a conjoint analysis study. Vaccine. 2011;29(27):4507-11.

[72] Hughes CC, Jones AL, Feemster KA, Fiks AG. HPV vaccine decision making in pediatric primary care: a semi-structured interview study. BMC Pediatr. 2011;11:74.

[73] Haesebaert J, Lutringer-Magnin D, Kalecinski J, Barone G, Jacquard AC, Regnier V, et al. French women's knowledge of and attitudes towards cervical cancer prevention and the acceptability of HPV vaccination among those with 14 - 18 year old daughters: a quantitative-qualitative study. BMC Public Health. 2012;12:1034.

[74] Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine. 2013;31(23):2638-46.

[75] Joint Committee on Vaccination and Immunisation (JCVI). JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK 2014 [updated 21 March 2014; cited 5 Sep 2017]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/252859/JCVI_MenB_Update.pdf.

[76] Lau JS, Adams SH, Boscardin WJ, Irwin CE, Jr. Young adults' health care utilization and expenditures prior to the Affordable Care Act. J Adolesc Health. 2014;54(6):663-71.

[77] Bernstein HH, Bocchini JA, Jr., Committee On Infectious D. Practical Approaches to Optimize Adolescent Immunization. Pediatrics. 2017;139(3).

[78] Pharmaceutical Benefits Advisory Committee. Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y(adolescents): Pre-filled syringe, 0.5mL; Nimenrix® Pharmaceutical Benefits Scheme,; 2018 [cited 25 October 2018]. Available from: http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Meningococcal-polysaccharide-conjugate-vaccine-adolescents-psd-march-2018.

[79] Marshall H, Ryan P, Roberton D, Beilby J. Varicella immunisation practice: Implications for provision of a recommended, non-funded vaccine. J Paediatr Child Health. 2009;45(5):297-303.

[80] Hart CA, Thomson AP. Meningococcal disease and its management in children. BMJ. 2006;333(7570):685-90.

[81] Rouphael NG, Stephens DS. Neisseria meningitidis: biology, microbiology, and epidemiology. Methods Mol Biol. 2012;799:1-20.

[82] Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. Vaccine. 2012;30 Suppl 2:B26-36.

[83] Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009;27 Suppl 2:B51-63.

[84] Lahra MM, Enriquez R. Australian Meningococcal Surveillance Programme annual report, 2016. Commun Dis Intell Q Rep. 2017;41(4):E369-E82.

[85] Tzanakaki G, Urwin R, Musilek M, Kriz P, Kremastinou J, Pangalis A, et al. Phenotypic and Genotypic Approaches to Characterization of Isolates of Neisseria meningitidis from Patients and Their Close Family Contacts. J Clin Microbiol. 2001;39(4):1235-40.

[86] Maiden MC, Bygraves JA, Feil E, Morelli G, Russell JE, Urwin R, et al. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. Proc Natl Acad Sci U S A. 1998;95(6):3140-5.

[87] Vyse A, Ellsbury G, Madhava H. Protecting UK adolescents and adults against meningococcal serogroup B disease. Expert Rev Vaccines. 2018;17(3):229-37.

[88] Australian Government Department of Health. Invasive Meningococcal Disease National Surveillance Report - With a focus on MenW - December 2017. Canberra: 2018 [updated 06 August 2018; cited 19 September 2018]. Available from: www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/31-Dec17-IMD-Surveillance-report.pdf.

[89] Australian Government Department of Health. Invasive Meningococcal Disease National Surveillance Report - With a focus on MenW - Quarter 2, 2018. Canberra: 2018 [updated 26 September 2018; cited 4 November 2018]. Available from: www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC4B495BDEC1CA25807D001327FA/$File/31-Mar18-IMD-Surveillance-report.pdf.

[90] Archer BN, Chiu CK, Jayasinghe SH, Richmond PC, McVernon J, Lahra MM, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999–2015: priority populations for vaccination. Med J Aust. 2017;207(9):382-7.

[91] Dey A, Knox S, Wang H, Beard FH, McIntyre PB. Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008-2011. Commun Dis Intell Q Rep. 2016;40 Suppl:S1-70.

[92] Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. Pediatrics. 1995;95(5):646-56.

[93] Guimont C, Hullick C, Durrheim D, Ryan N, Ferguson J, Massey P. Invasive meningococcal disease--improving management through structured review of cases in the Hunter New England area, Australia. J Public Health (Oxf). 2010;32(1):38-43.

[94] Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. J Hyg (Lond). 1983;90(1):49-54.

[95] Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. J Paediatr Child Health. 1999;35(1):42-8.

[96] Wang B, Clarke M, Thomas N, Howell S, Afzali HH, Marshall H. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. Pediatr Infect Dis J. 2014;33(3):316-8.

[97] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine. 2014;32(37):4791-8.

[98] Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. 2012;11(9):774-83.

[99] Mensch A, Beck T, Civello D, Kunigkeit C, Lachmann N, Stock S, et al. Applying GRADE Criteria to Clinical Inputs to Cost-Effectiveness Modeling Studies. Pharmacoeconomics. 2018;36(8):987-94.

[100] Howitz M, Lambertsen L, Simonsen JB, Christensen JJ, Molbak K. Morbidity, mortality and spatial distribution of meningococcal disease, 1974-2007. Epidemiol Infect. 2009;137(11):1631-40.

[101] Darton T, Guiver M, Naylor S, Jack DL, Kaczmarski EB, Borrow R, et al. Severity of meningococcal disease associated with genomic bacterial load. Clin Infect Dis. 2009;48(5):587-94.

[102] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J. 2013;32(1):e20-5.

[103] Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis. 2011;53(9):e117-24.

[104] Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. Hum Vaccin. 2011;7(4):458-65.

[105] Karve S, Misurski D, Miller J, Davis KL. Costs of sequelae associated with invasive meningococcal disease: Findings from a US managed care population. Health Outcomes Res Med. 2011;2(4):e215-e26.

[106] Fellick JM, Sills JA, Marzouk O, Hart CA, Cooke RW, Thomson AP. Neurodevelopmental outcome in meningococcal disease: a case-control study. Arch Dis Child. 2001;85(1):6-11.

[107] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis. 2015;60(8):e27-35.

[108] Stoof SP, Rodenburg GD, Knol MJ, Rumke LW, Bovenkerk S, Berbers GA, et al. Disease Burden of Invasive Meningococcal Disease in the Netherlands Between June 1999 and June 2011: A Subjective Role for Serogroup and Clonal Complex. Clin Infect Dis. 2015;61(8):1281-92.

[109] Healy CM, Butler KM, Smith EO, Hensey OP, Bate T, Moloney AC, et al. Influence of serogroup on the presentation, course, and outcome of invasive meningococcal disease in children in the Republic of Ireland, 1995-2000. Clin Infect Dis. 2002;34(10):1323-30.

[110] Harrison LH, Pass MA, Mendelsohn AB, Egri M, Rosenstein NE, Bustamante A, et al. Invasive meningococcal disease in adolescents and young adults. JAMA. 2001;286(6):694-9.

[111] Buysse CM, Oranje AP, Zuidema E, Hazelzet JA, Hop WC, Diepstraten AF, et al. Long-term skin scarring and orthopaedic sequelae in survivors of meningococcal septic shock. Arch Dis Child. 2009;94(5):381-6.

[112] Buysse CM, Vermunt LC, Raat H, Hazelzet JA, Hop WC, Utens EM, et al. Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care. 2010;14(3):R124.

[113] Bache CE, Torode IP. Orthopaedic sequelae of meningococcal septicemia. J Pediatr Orthop. 2006;26(1):135-9.

[114] Cabellos C, Nolla JM, Verdaguer R, Pelegrin I, Ribera A, Ariza J, et al. Arthritis related to systemic meningococcal disease: 34 years' experience. Eur J Clin Microbiol Infect Dis. 2012;31(10):2661-6.

[115] Tsolia MN, Theodoridou M, Tzanakaki G, Vlachou V, Mostrou G, Stripeli F, et al. Invasive meningococcal disease in children in Greece: comparison of serogroup A disease with disease caused by other serogroups. Eur J Clin Microbiol Infect Dis. 2006;25(7):449-56.

[116] McMillan M, Rokkas P, Angliss M, Buttery J, Marshall H. The Long-term Impact of Invasive Meningococcal Disease (IMD) in Australian Adolescents. 16th National Immunisation Conference: 4-6 June 2018; Adelaide, South Australia.

[117] Vermunt LC, Buysse CM, Joosten KF, Duivenvoorden HJ, Hazelzet JA, Verhulst FC, et al. Survivors of septic shock caused by Neisseria meningitidis in childhood: psychosocial outcomes in young adulthood. Pediatr Crit Care Med. 2011;12(6):e302-9.

[118] Vermunt LC, Buysse CM, Joosten KF, Hazelzet JA, Verhulst FC, Utens EM. Behavioural, emotional, and post-traumatic stress problems in children and adolescents, long term after septic shock caused by Neisseria meningitidis. Br J Clin Psychol. 2008;47(Pt 3):251-63.

[119] Vermunt LC, Buysse CM, Joosten KF, Oranje AP, Hazelzet JA, Verhulst FC, et al. Self-esteem in children and adolescents after septic shock caused by Neisseria meningitidis: scars do matter. J Adolesc Health. 2008;42(4):386-93.

[120] Vermunt LC, Buysse CM, Joosten KF, Hazelzet JA, Verhulst FC, Utens EM. Recovery in parents of children and adolescents who survived septic shock caused by Neisseria meningitidis: a cross-sectional study. Intensive Crit Care Nurs. 2010;26(3):128-37.

[121] Hadzic E, Sinanovic O, Memisevic H. Is Bacterial Meningitis a Risk Factor for Developing Attention Deficit Hyperactivity Disorder. Isr J Psychiatry Relat Sci. 2017;54(2):54-7.

[122] Ward K, Quinn H, Bachelor M, Bryant V, Campbell-Lloyd S, Newbound A, et al. Adolescent school-based vaccination in Australia. Commun Dis Intell Q Rep. 2013;37(2):E156-67.

[123] Cates JR, Shafer A, Carpentier FD, Reiter PL, Brewer NT, McRee AL, et al. How parents hear about human papillomavirus vaccine: implications for uptake. J Adolesc Health. 2010;47(3):305-8.

[124] Christensen H, Irving T, Koch J, Trotter CL, Ultsch B, Weidemann F, et al. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero((R)) to reduce meningococcal group B disease in Germany. Vaccine. 2016;34(29):3412-9.

[125] De Wals P, Zhou Z. Cost-effectiveness Comparison of Monovalent C Versus Quadrivalent ACWY Meningococcal Conjugate Vaccination in Canada. Pediatr Infect Dis J. 2017;36(7):e203-e7.

[126] Delea TE, Weycker D, Atwood M, Neame D, Alvarez FP, Forget E, et al. Cost-effectiveness of alternate strategies for childhood immunization against meningococcal disease with monovalent and quadrivalent conjugate vaccines in Canada. PloS One. 2017;12(5):e0175721.

[127] Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero(R)) against

meningococcal B disease: A cost-effectiveness analysis. Hum Vaccin Immunother. 2016;12(8):2148-61.

[128] Hepkema H, Pouwels KB, van der Ende A, Westra TA, Postma MJ. Meningococcal serogroup A, C, W(1)(3)(5) and Y conjugated vaccine: a cost-effectiveness analysis in the Netherlands. PloS One. 2013;8(5):e65036.

[129] Lecocq H, Parent du Chatelet I, Taha MK, Levy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine. 2016;34(19):2240-50.

[130] Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GP, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: Crucial impact of changes in incidence. Hum Vaccin Immunother. 2013;9(5):1129-38.

[131] Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new MenB vaccine (Bexsero) into the Italian routine infant immunisation programme. PloS One. 2015;10(4):e0123383.

[132] De Wals P, Coudeville L, Trottier P, Chevat C, Erickson LJ, Nguyen VH. Vaccinating adolescents against meningococcal disease in Canada: a cost-effectiveness analysis. Vaccine. 2007;25(29):5433-40.

[133] Hanquet GC, Agnew E, Trotter, Robays J, Dubois, Devriese S, et al. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study. Health Technology Assessment (HTA). 2014;KCE Reports 231.

[134] Tu HA, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, et al. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. Vaccine. 2014;32(42):5436-46.

[135] Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012;15(6):812-20.

[136] Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. Value Health. 2012;15(6):804-11.

[137] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.

[138] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value Health. 2012;15(6):843-50.

[139] Caro JJ, Briggs AH, Siebert U, Kuntz KM, Force I-SMGRPT. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. Value Health. 2012;15(6):796-803.

[140] Erickson LJ, De Wals P, McMahon J, Heim S. Complications of meningococcal disease in college students. Clin Infect Dis. 2001;33(5):737-9.

[141] Cohen E, Berry JG, Camacho X, Anderson G, Wodchis W, Guttmann AJP. Patterns and costs of health care use of children with medical complexity. Pediatrics. 2012;130(6):e1463-70.